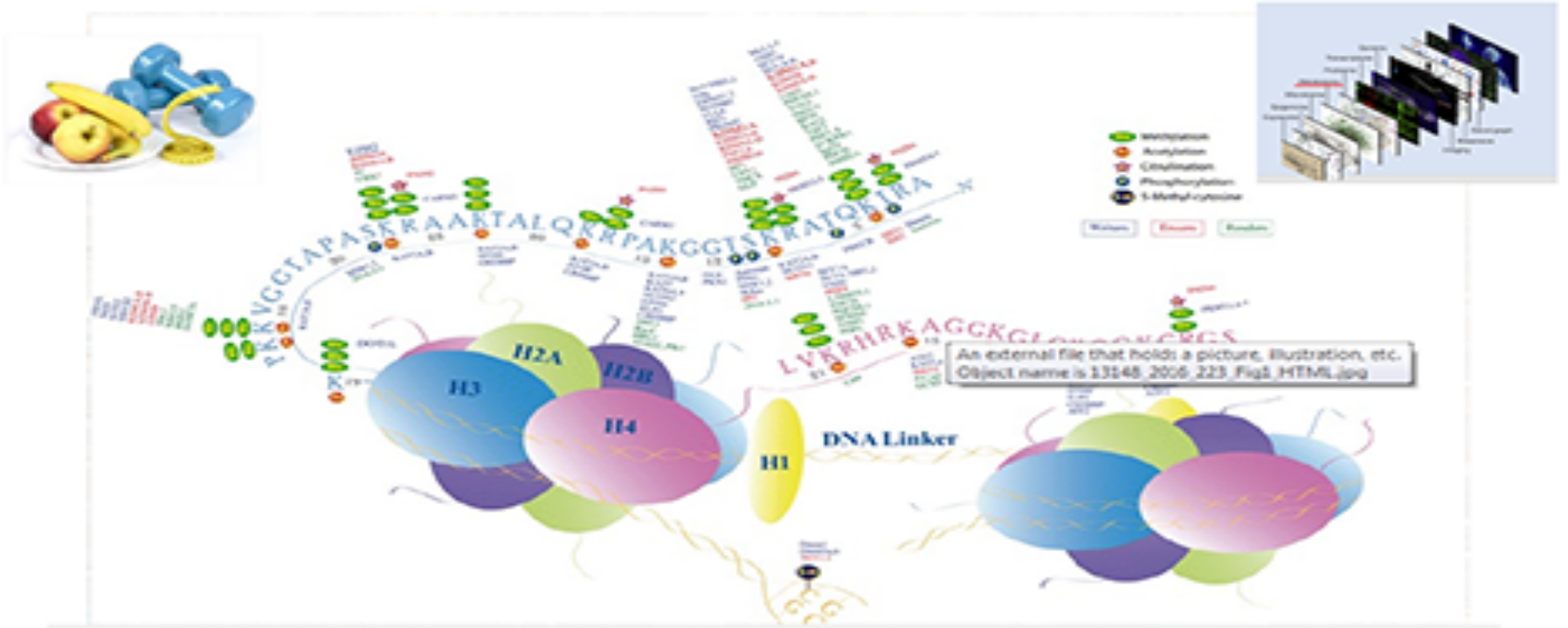
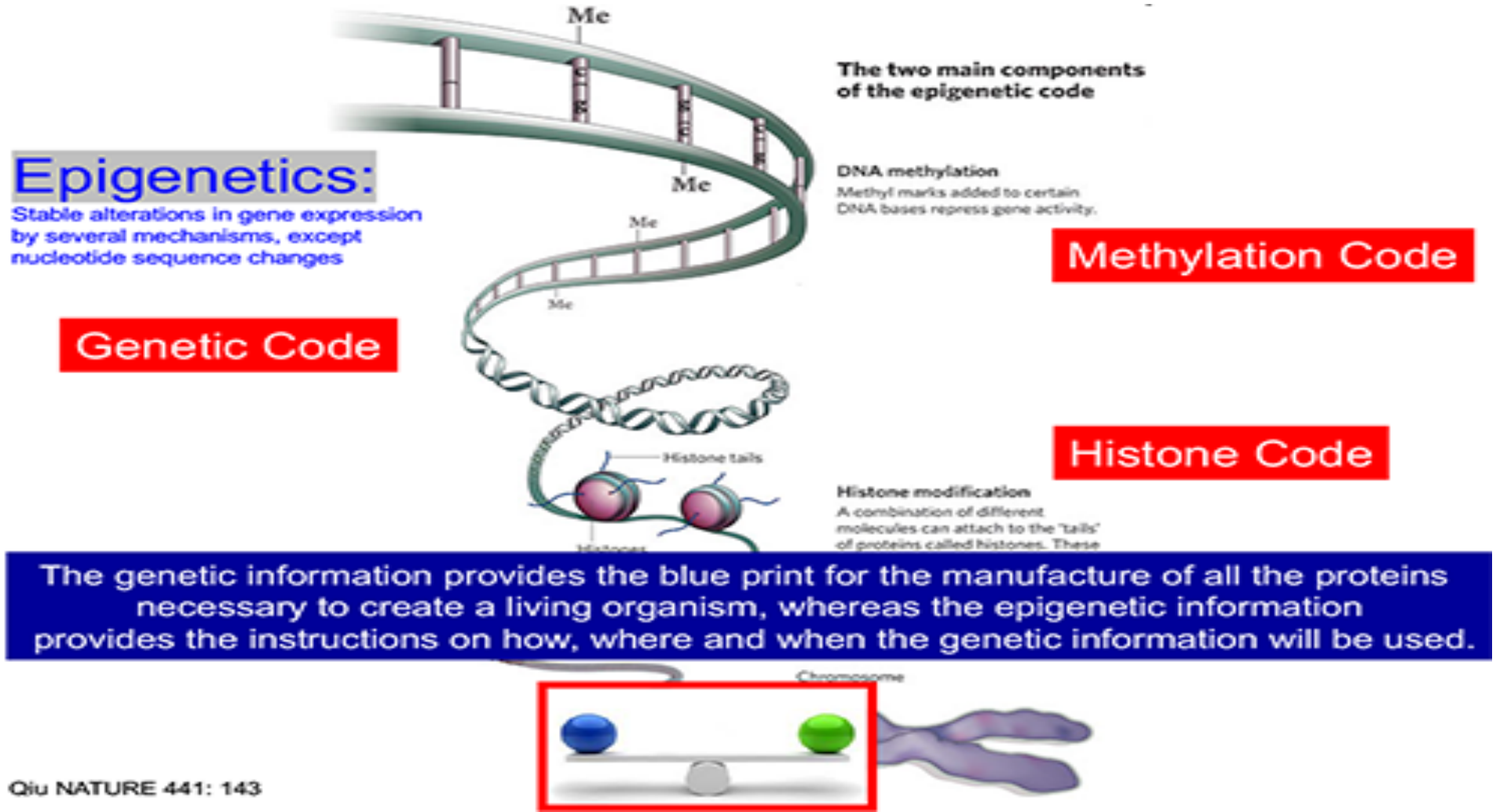
Epigenetics

EPIGENETICS IN CANCER CONTROL AND PREVENTION: ARE WE READY FOR THE PRIME TIME?



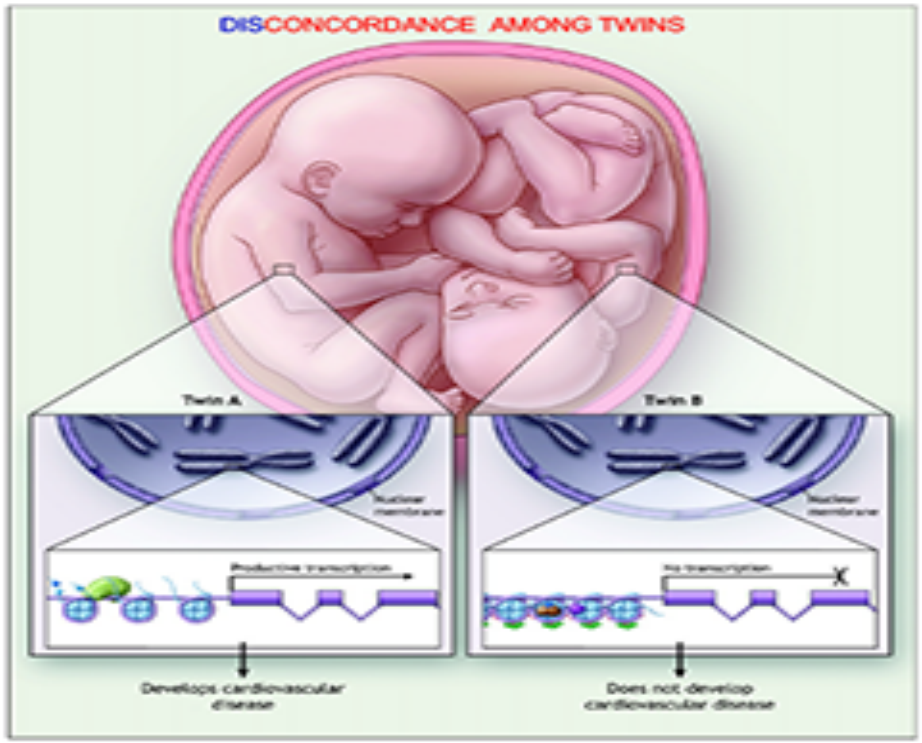
Mukesh Verma, Ph.D.
Chief, Methods and Technologies Branch
Program Director,
Epidemiology and Genomics Res. Program
DCCPS, NCI, NIH

Epigenetics



DNA and destiny

The choices you make
can change your genes
-- and those of your kids.



Epigenetic predisposition to angiogenesneis? Individual? Populations?

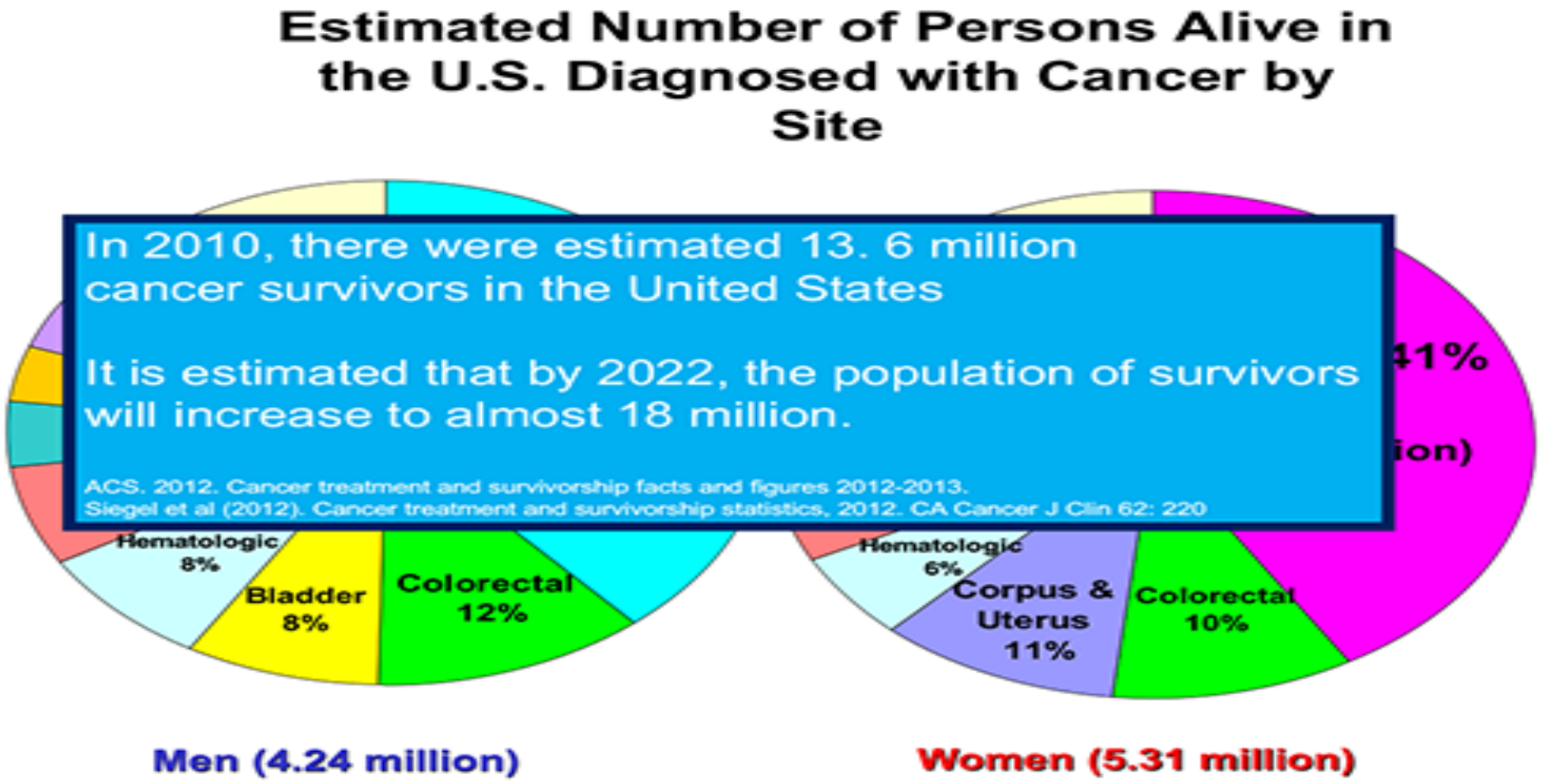
Pharmacogenomics and pharmacoepigenomics (personalized medicine)

Microenvironment, microbiome, and gene expression

GWAS and EWAS

Adapted from Matouk and Marsden Cir Res 102:873

Cancer Survivors



Cancer continuum

DCCPS covers cancer continuum

Prevention

Tobacco, physical activity, diet, sun, environment, HPV immunization

Early Detection

Breast, cervical, colorectal cancer screening

Diagnosis

Incidence, Stage at diagnosis

Treatment

Trends in cancer treatment

Life After Cancer

Financial burden of cancer care, Cancer survivorship

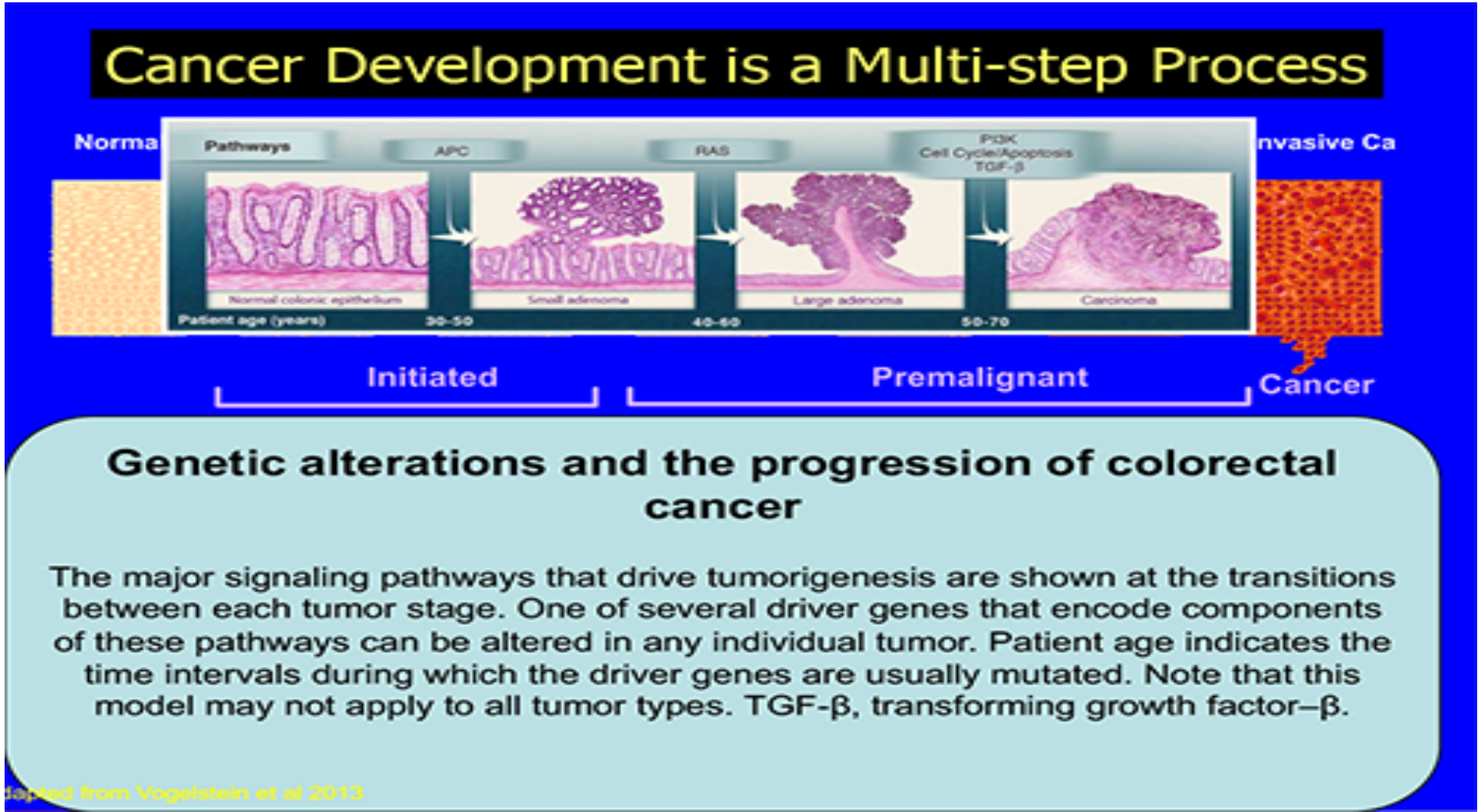
End of Life

Mortality, Person – years of life lost

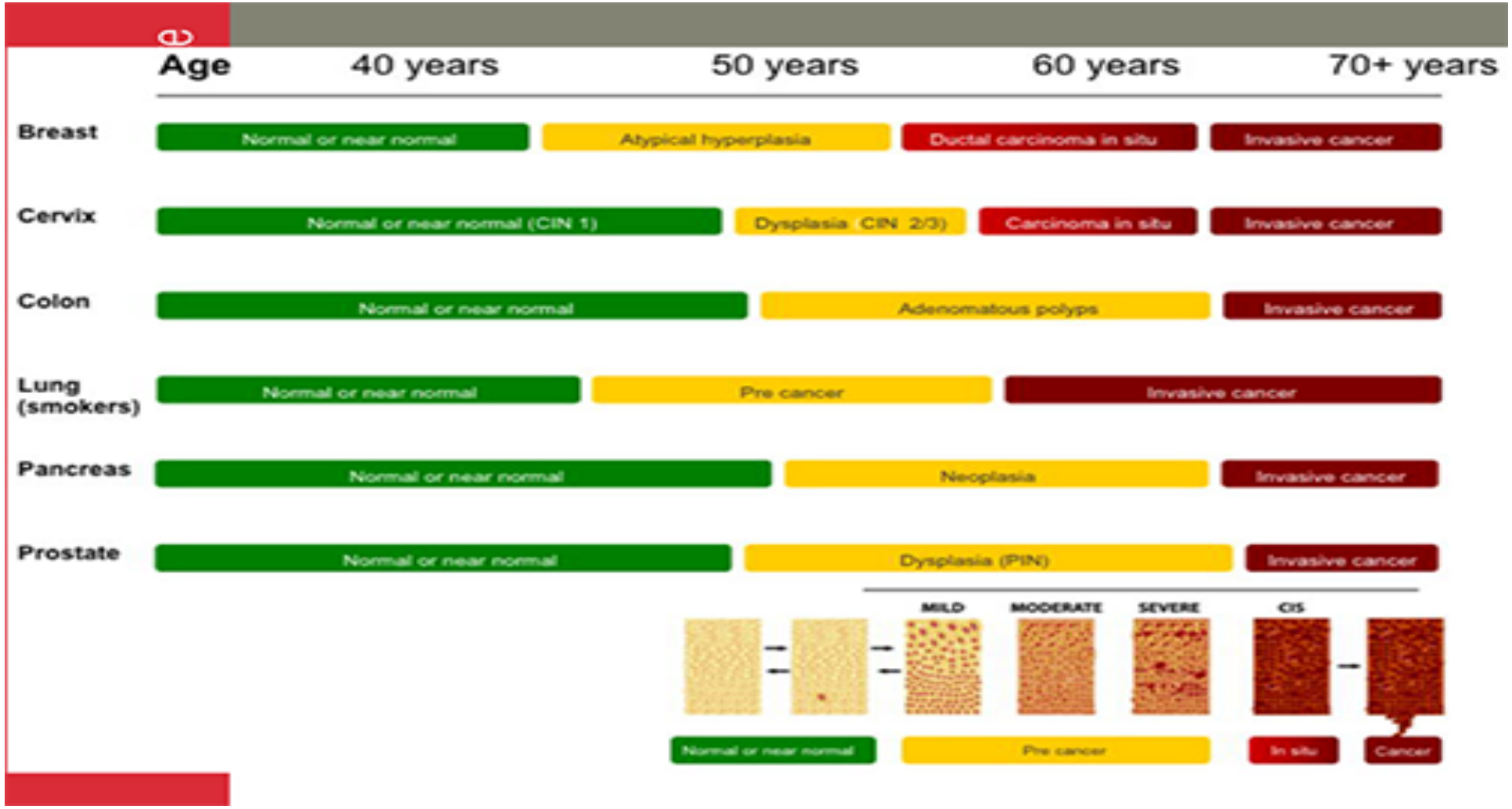
Prevention → Cancer recurrence, Secondary cancer

Prevention: restoring transcription, halting progression, or stopping metastasis

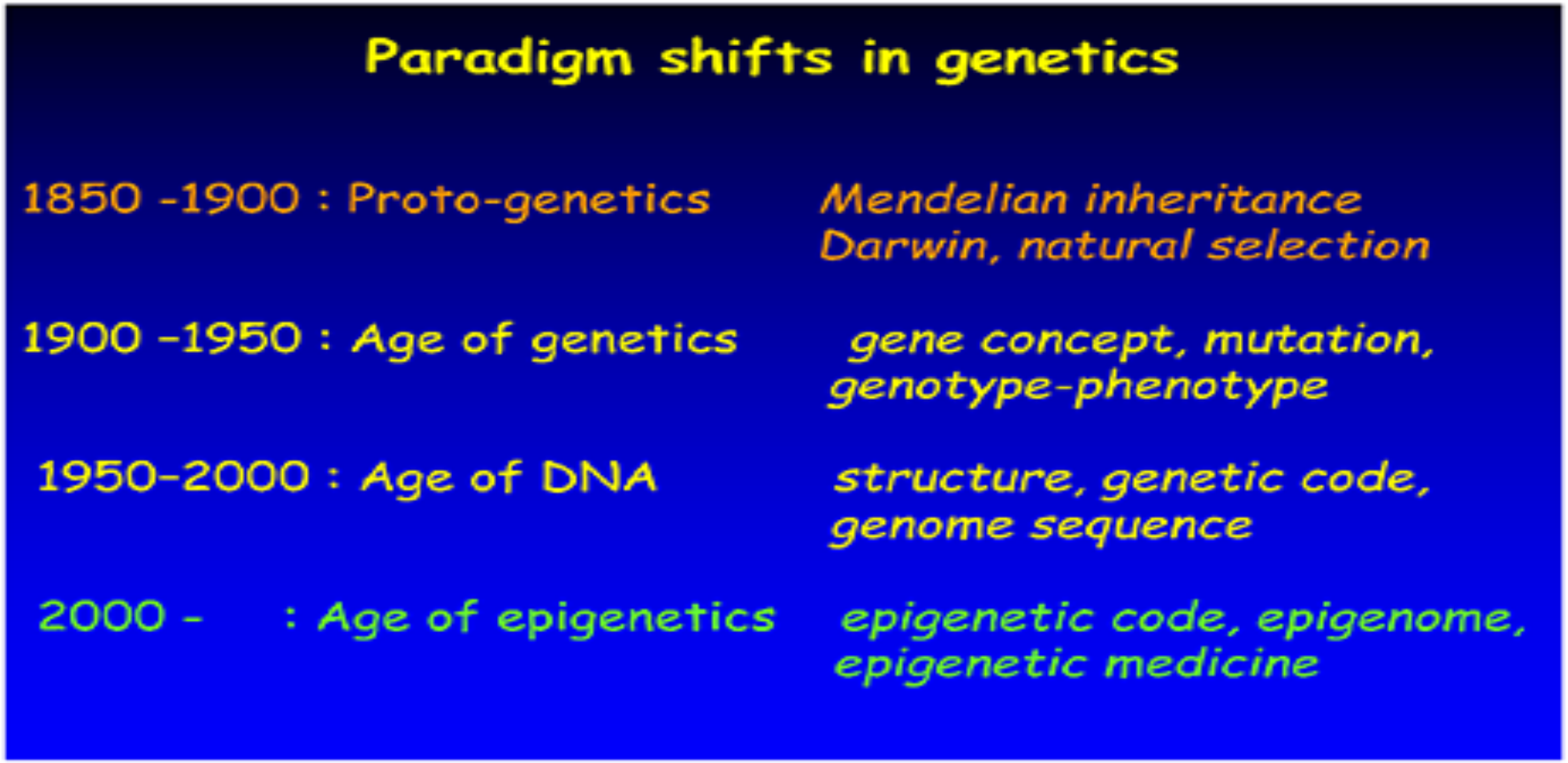
Cancer development



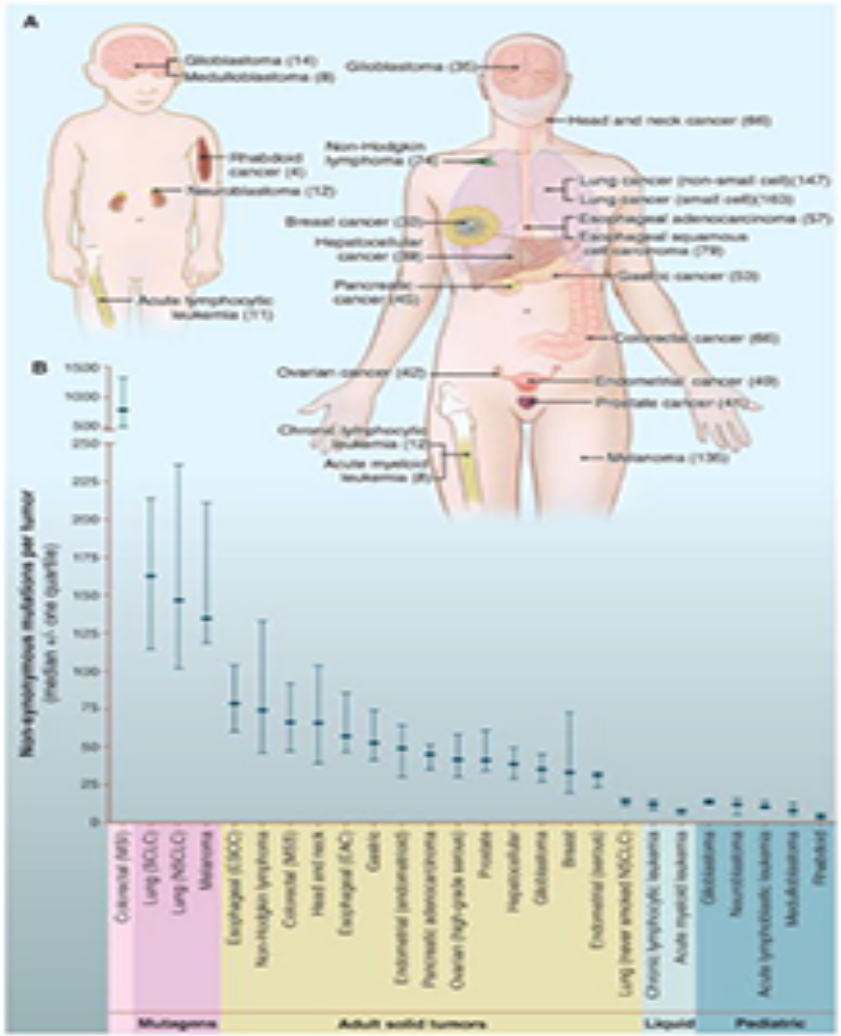
Cancer and age



Paradigm shift



Genome landscape



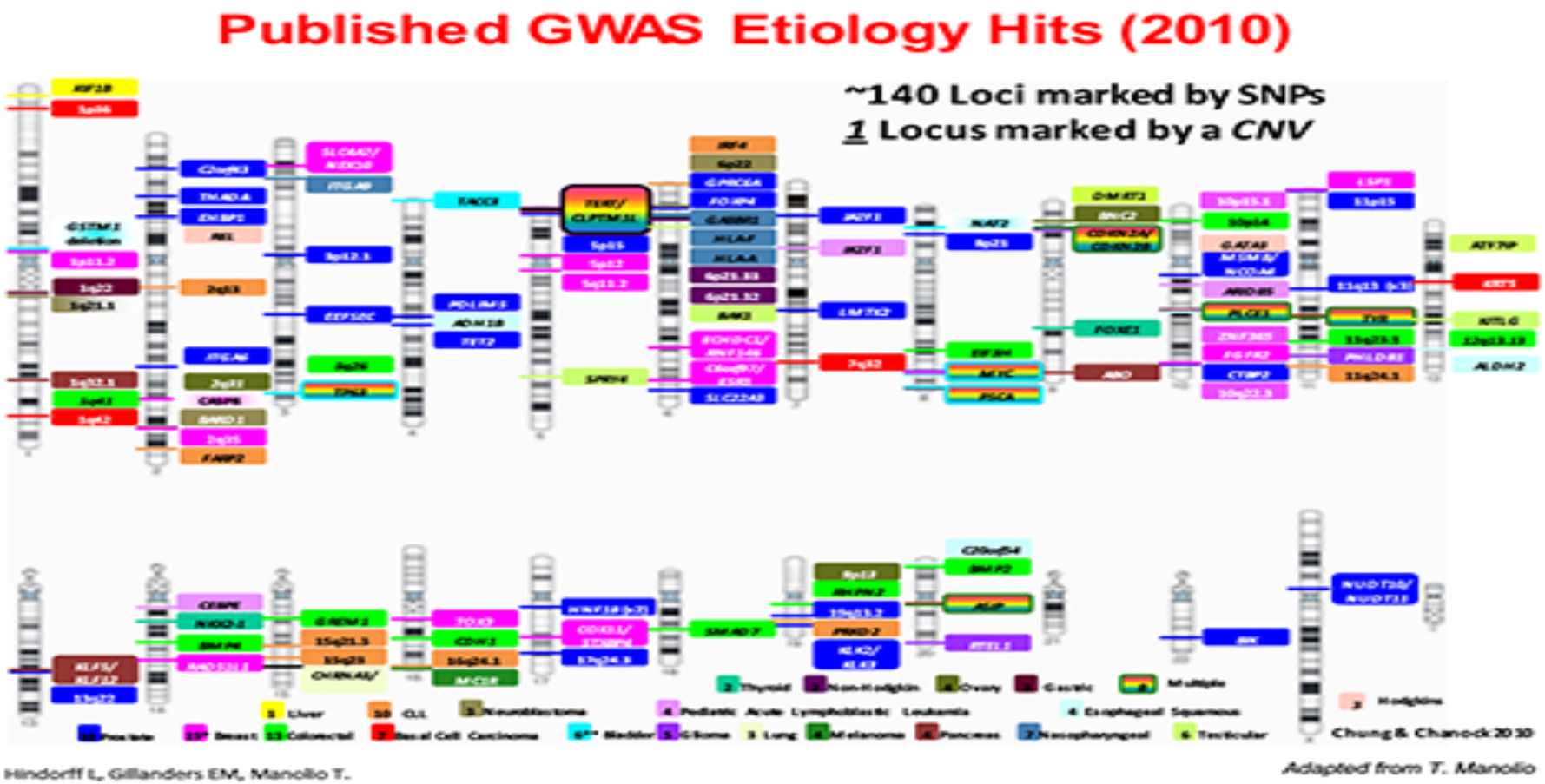
CANCER GENOME LANDSCAPE

Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Adapted from Vogelstein and Kinzler (Science 2013)

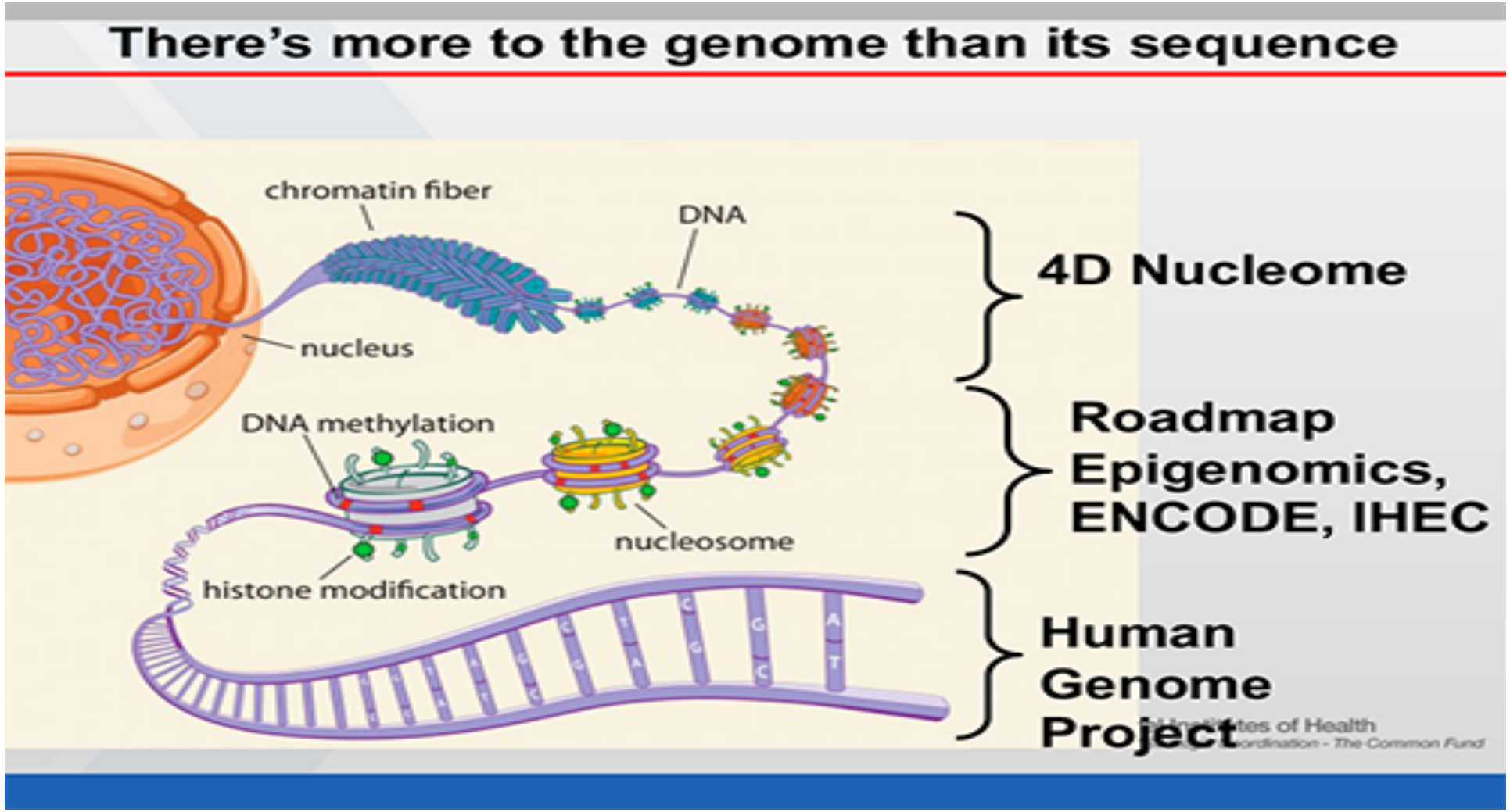
Cancer genes

GWAS hits


Published GWAS Etiology Hits (2010)
~140 Loci marked by SNPs
1 Locus marked by a CNV
Chung & Chanock 2010
Hindorff L, Gillanders EM, Manolio T.
Adapted from T. Manolio

Genome wide associations

Genome sequence



Kornberg and nucleosome

Nucleosomes (Units of Chromatin)

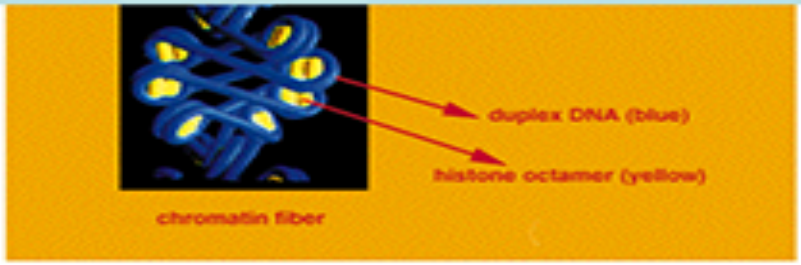
DNA
Histones H2a, H2b, H3, H4

To neutralize charge and provide stability

H1 is a linker histone which binds to the DNA linking two adjacent nucleosomal cores

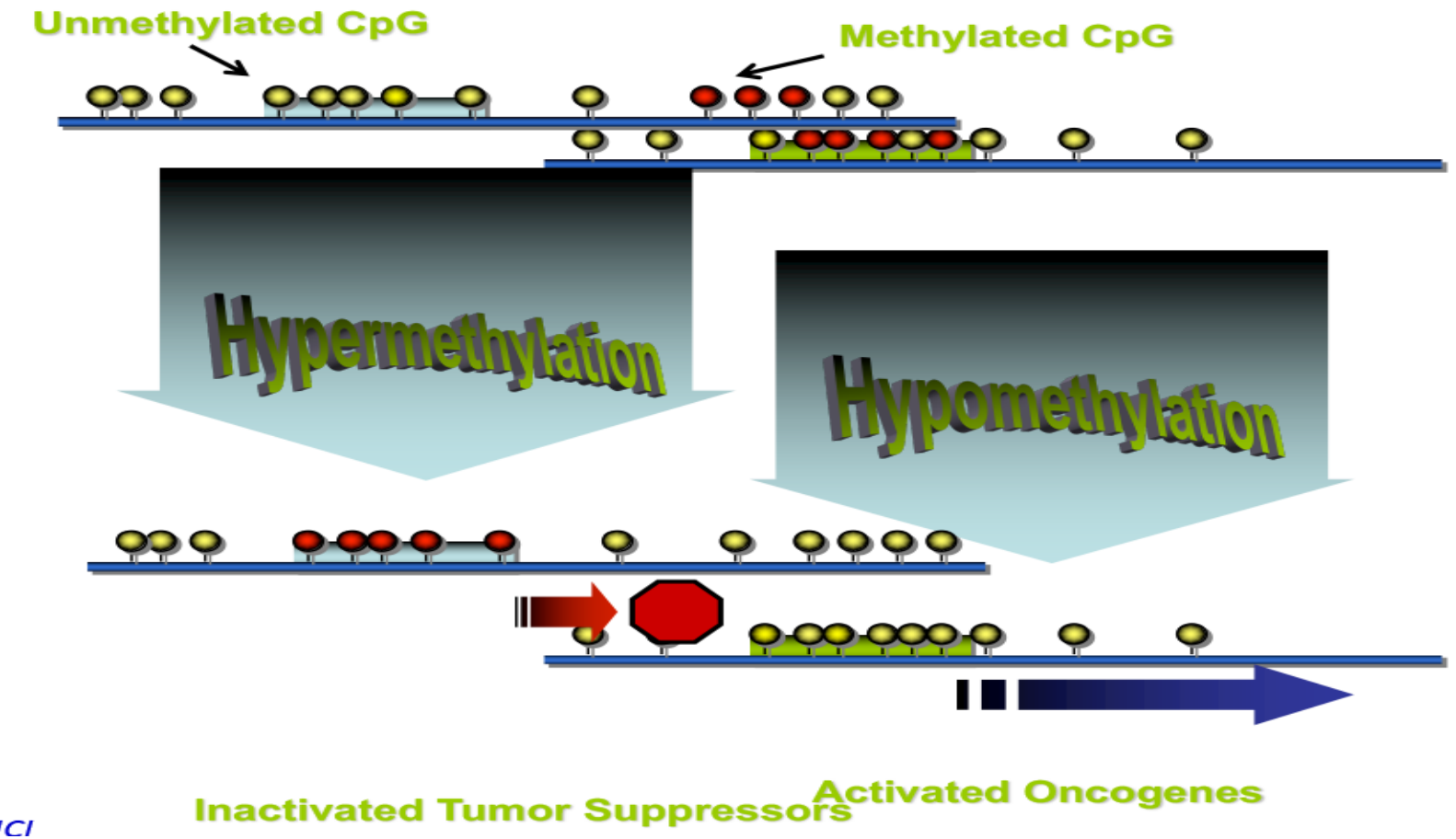
Nucleosome: two turns of DNA (146 base pairs) wrapped around an octomeric complex of two of each of histone types

1974: Roger Kornberg discovers nucleosome who won Nobel Prize in 2006.

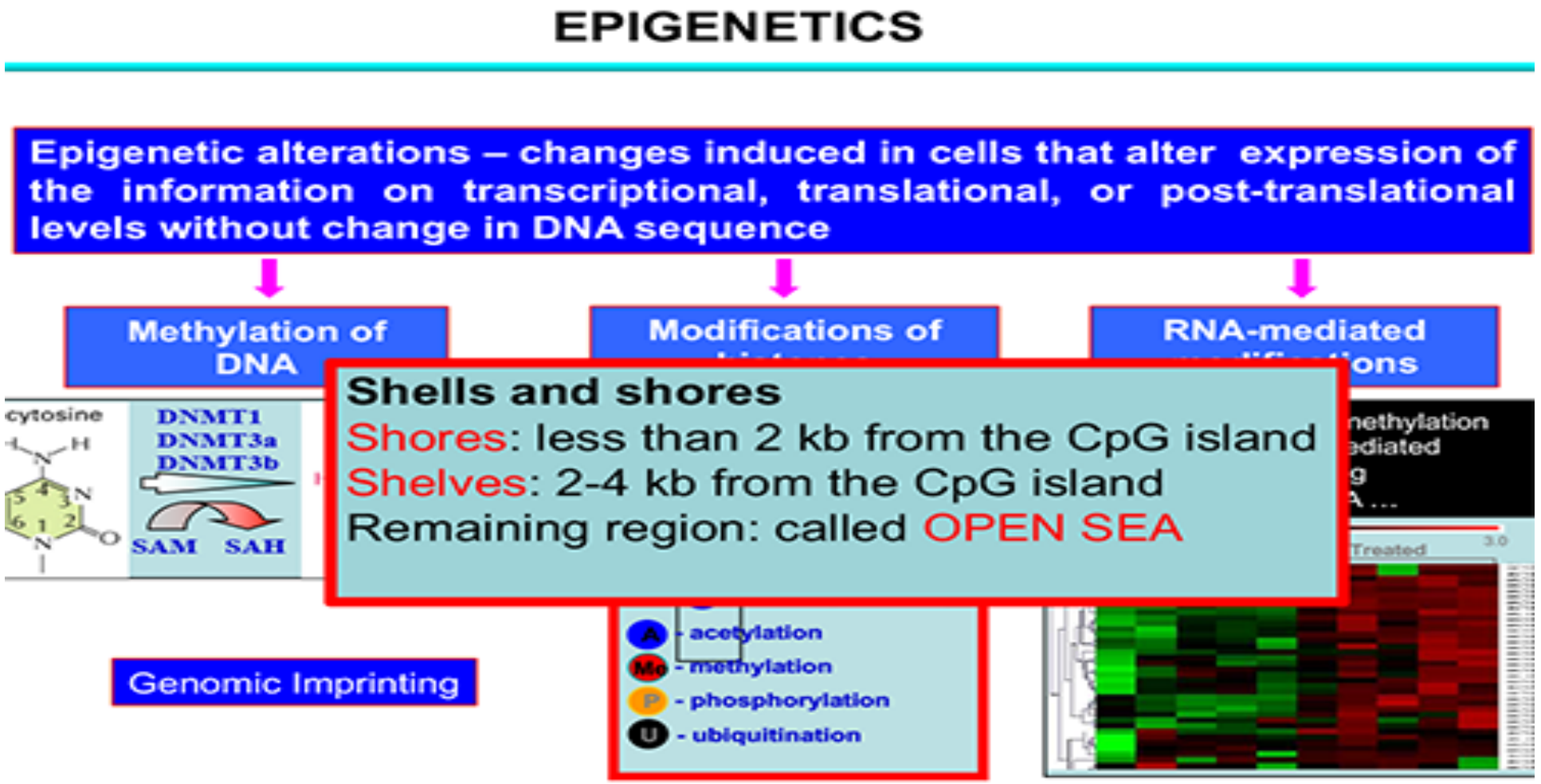


Shores are 0-2kb from islands
Shelves are 2-4 kb and enhancers are beyond shelves

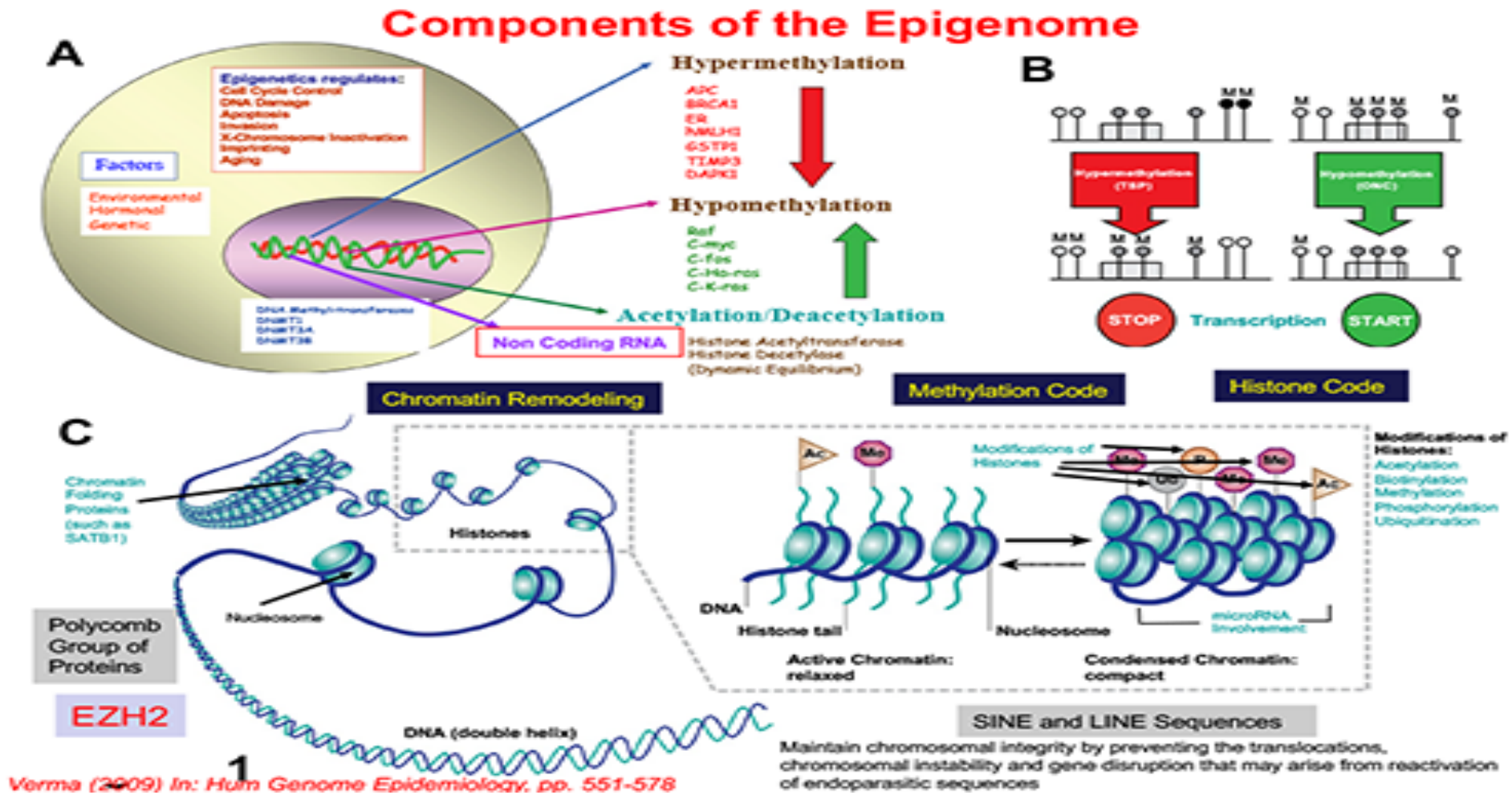
DNA methylation



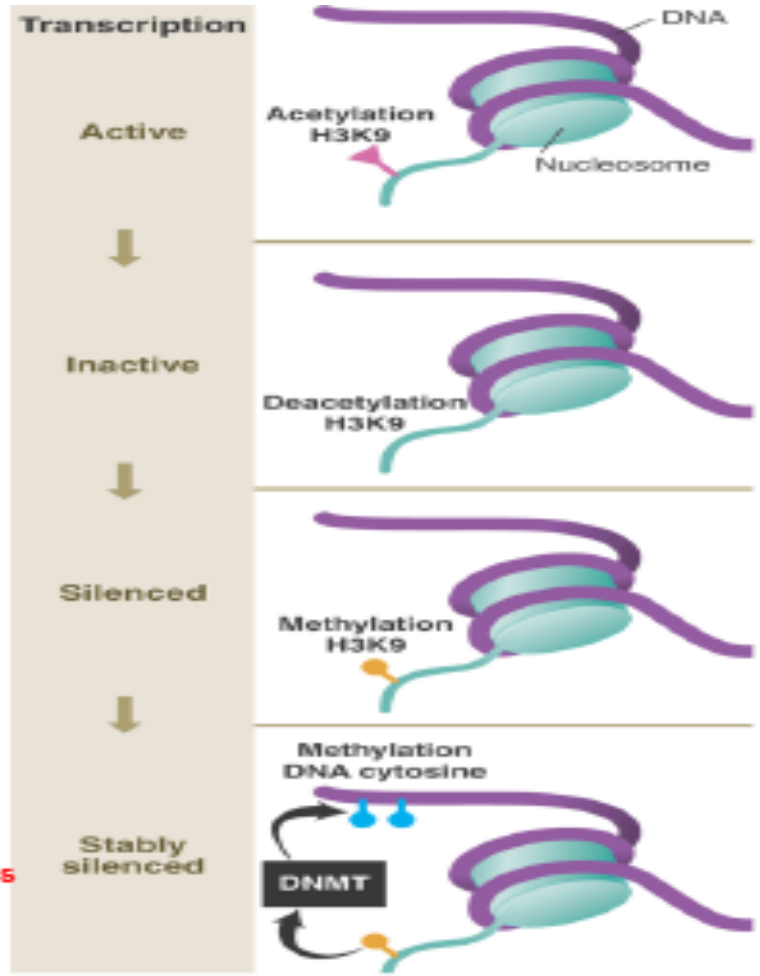
Epigenetics



Epigenome components

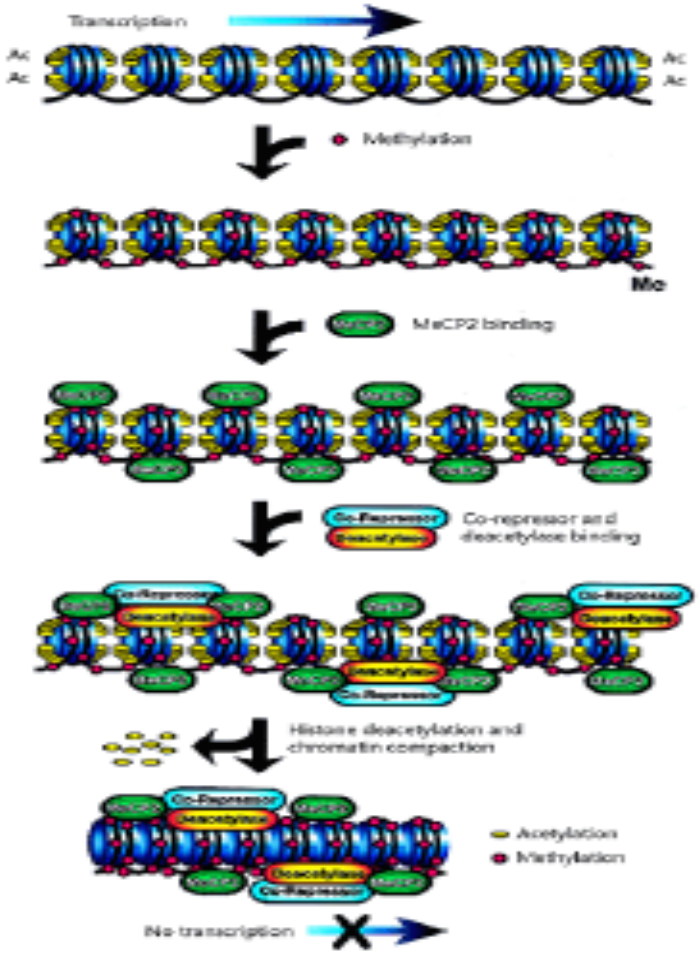


Methylation



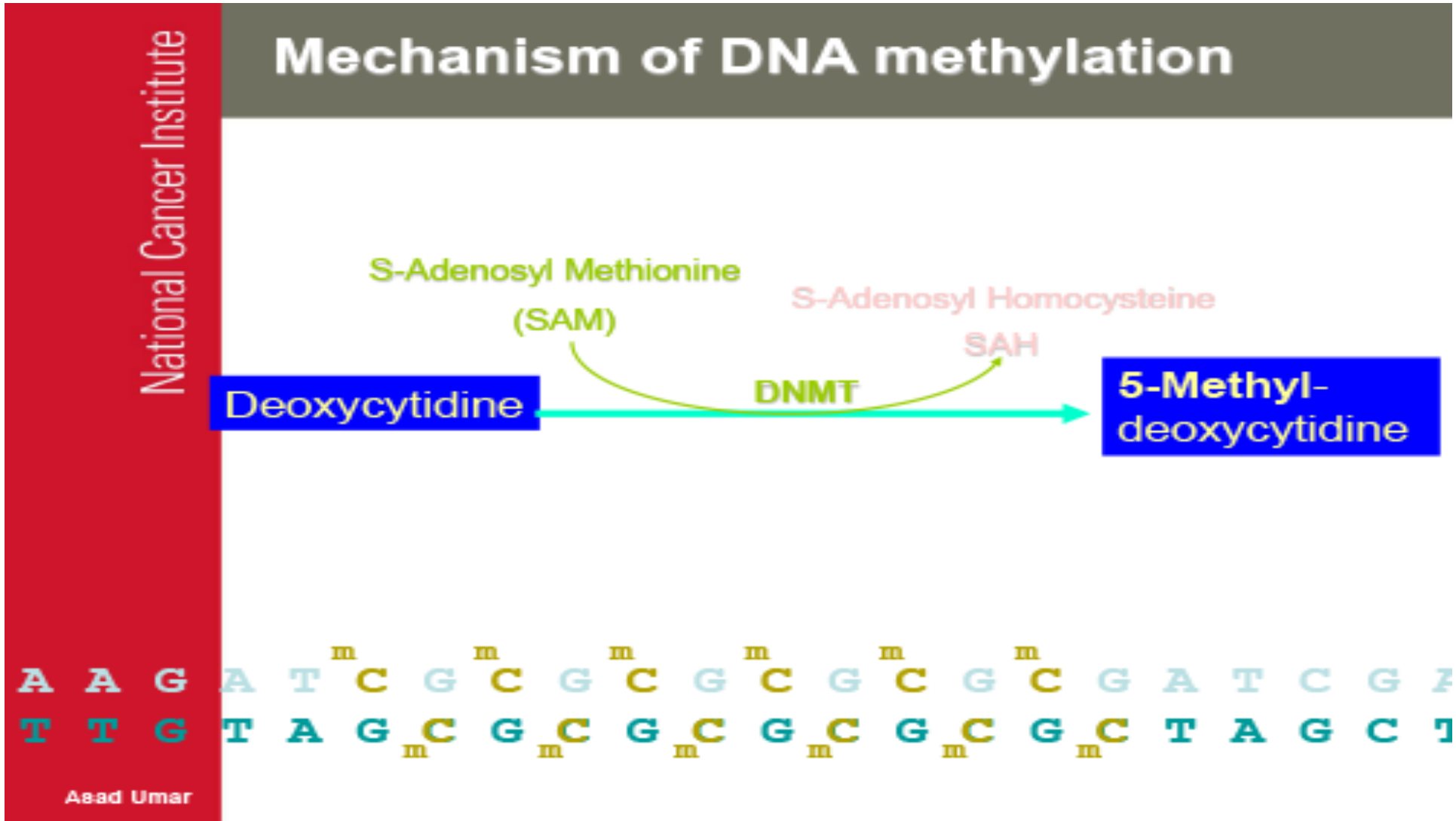
Peter Jones

Andrew Feinberg



Jones and Laird. *Nat Rev Gen* 21: 163

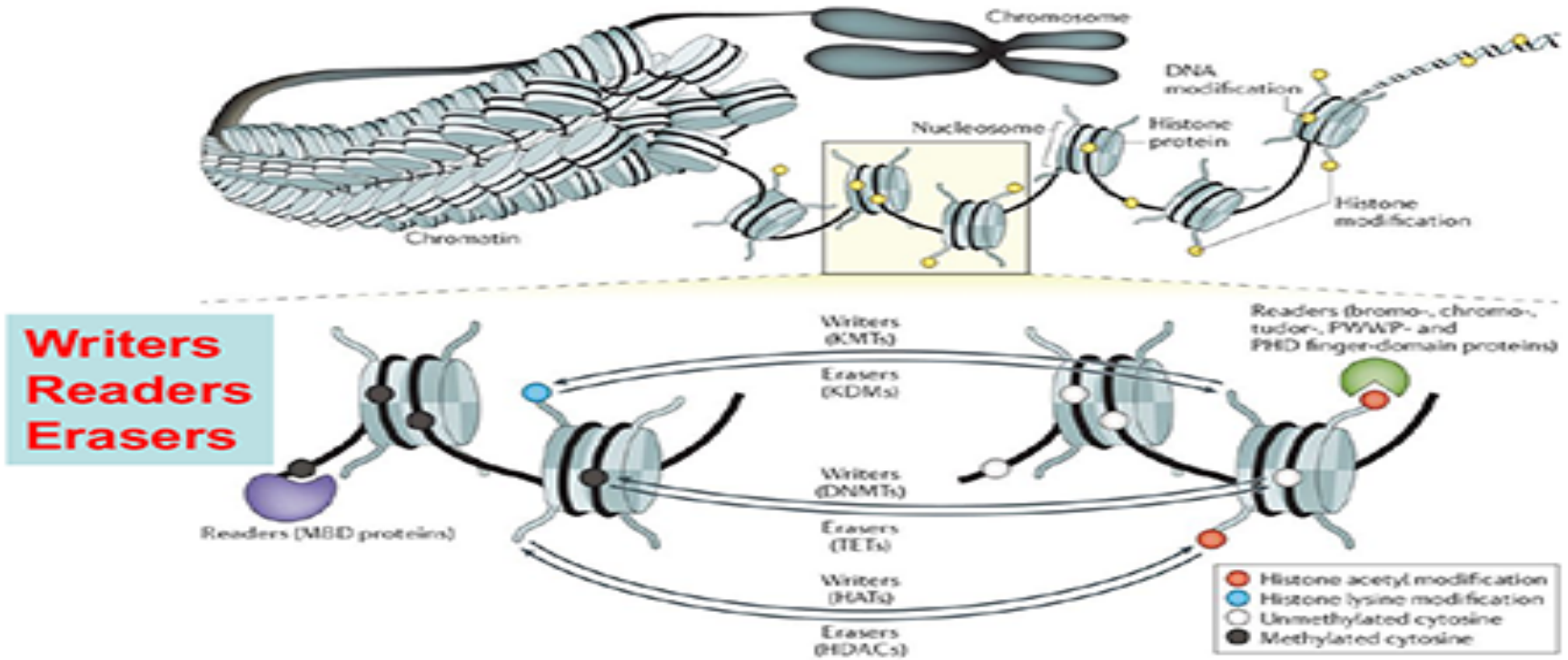
Mechanism


National Cancer Institute
Mechanism of DNA methylation
S-Adenosyl Methionine
(SAM)
S-Adenosyl Homocysteine
SAH
Deoxycytidine
DNMT
5-Methyl-
deoxycytidine
Asad Umar

Chromatin modifications

Figure 1 : Modulation of covalent modifications on chromatin.

From: Targeting the cancer epigenome for therapy



Ten-eleven translocation (TET) family of 5-methylcytosine oxidases.

Exercise


Exercise is important for everyone
portant?
changes
life+style
DIET
• Drug targeting
You only need to sequence your genome once, but you need to determine your epigenome multiple times...
https://www.youtube.com/watch?v=JMT6oRYgkTk

Environment and development

E-cigarette vapors

Vaping can damage vital immune system

OPEN ACCESS

ORIGINAL ARTICLE

Pro-inflammatory effects of e-cigarette vapour condensate on human alveolar macrophages

Aaron Scott,[1] Sebastian T Lugg,[1] Kerrie Aldridge,[1] Keir E Lewis,[2] Allen Bowden,[3] Rahul Y Mahida,[1] Frances Susanna Grudzinska,[1] Davinder Dosanjh,[1] Dhruv Parekh,[1] Robert Foronjy,[4] Elizabeth Sapey,[1] Babu Naidu,[1] David R Thickett[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2018-211663).

[1]Birmingham Acute Care Research Group, Institute of Inflammation and Ageing (IIA), University of Birmingham, Birmingham, UK
[2]College of Medicine, Swansea

ABSTRACT

Objective Vaping may increase the cytotoxic effects of e-cigarette liquid (E-CL). We compared the effect of unvaped E-CL to e-cigarette vapour condensate (ECVC) on alveolar macrophage (AM) function.

Methods AMs were treated with ECVC and nicotine-free ECVC (nfECVC). AM viability, apoptosis, necrosis, cytokine, chemokine and protease release, reactive oxygen species (ROS) release and bacterial phagocytosis were assessed.

Key messages

What is the key question?

► Do e-cigarettes have a negative impact on alveolar macrophage viability and function?

What is the bottom line?

► Vapourised e-cigarette fluid is cytotoxic, pro-inflammatory and inhibits phagocytosis in alveolar macrophages.

Thorax: first published as 10.1136/thoraxjnl-2018-211663 on

Cancer etiology

Understanding Cancer Etiology and Risk Assessment

Need healthy population (pathologically disease free) (cohort) with information about

- Exposure (Chemicals, Radiations, Infectious Agents, Toxic substance)
- Family History
- Diet and Life Style
- Medication

Need easily collected biospecimens (non-invasive technologies) and analytic tools

Need follow up (for longitudinal studies) for several years

Challenge: Expensive, data sharing

Advantage: Essential to identify risk factors for cancer

EGRP studies

29

EGRP Studies Are Everywhere

- Senegal
- Malawi
- The Zambia
- China
- Japan
- Egypt
- Israel
- Brazil
- Colombia
- England
- Canada
- Sweden
- Denmark
- France
- Costa Rica
- Singapore
- Poland
- Australia
- U.S., including Alaska & Hawaii

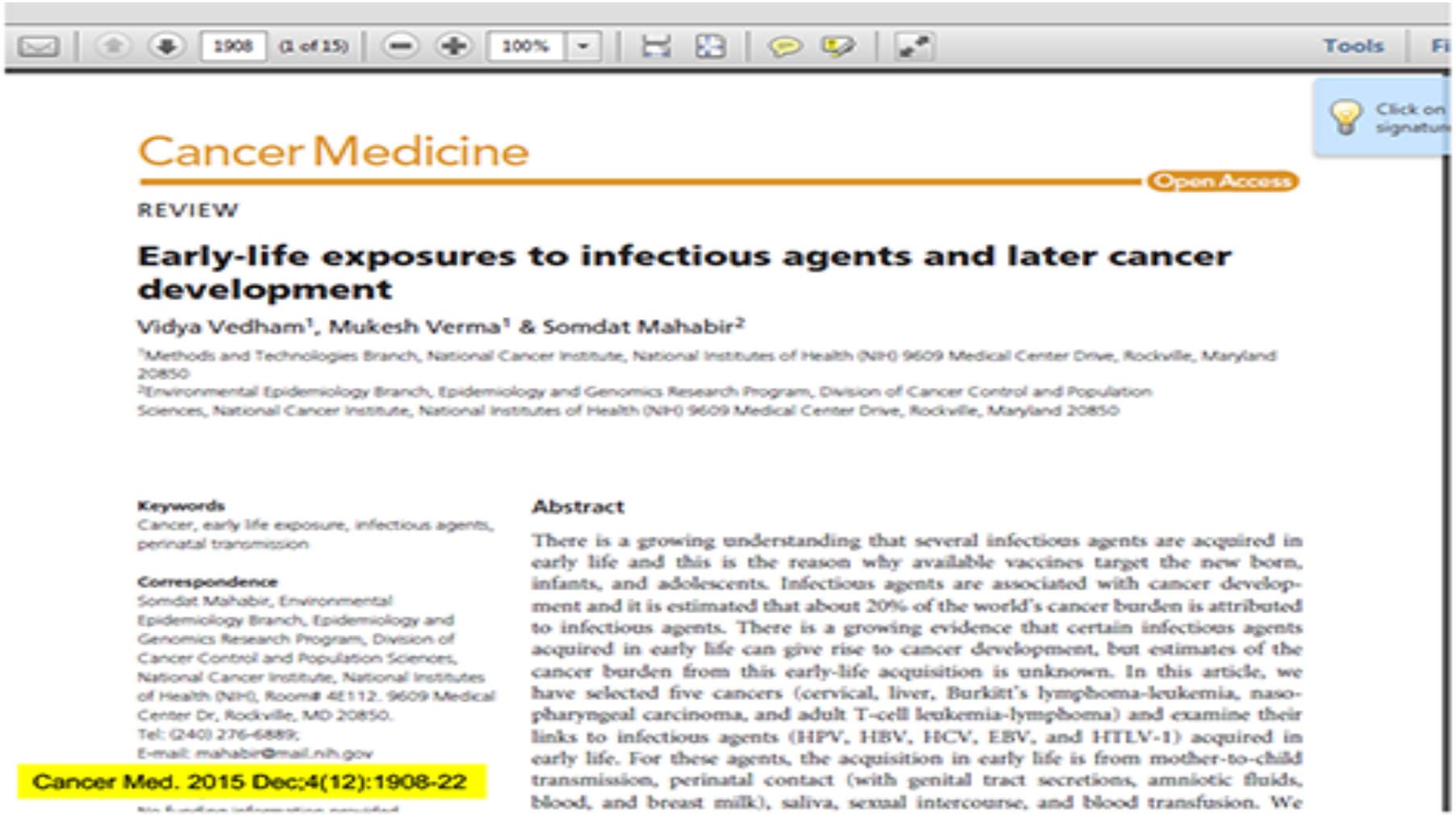
2.3 Million Subjects

Cohorts, CGN and Family Registries

Cohort consortium

- 62 cohorts, over 4 million individuals
- Membership: cohort studies worldwide with >10,000 subjects, blood samples and questionnaire data on important cancer risk factors
- The Cohort Consortium was formed by NCI to address the need for large-scale collaborations for
  - Rapid identification and confirmation of common polymorphisms and cancer susceptibility (GWAS)
  - Studies of GxG and GxE interactions in the etiology of cancer.

Early life exposure



Cancer Medicine

Open Access

REVIEW

Early-life exposures to infectious agents and later cancer development

Vidya Vedham[1], Mukesh Verma[1] & Somdat Mahabir[2]

[1]Methods and Technologies Branch, National Cancer Institute, National Institutes of Health (NIH) 9609 Medical Center Drive, Rockville, Maryland 20850

[2]Environmental Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH) 9609 Medical Center Drive, Rockville, Maryland 20850

Keywords
Cancer, early life exposure, infectious agents, perinatal transmission

Correspondence
Somdat Mahabir, Environmental Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health (NIH), Room# 4E112, 9609 Medical Center Dr, Rockville, MD 20850.
Tel: (240) 276-6889;
E-mail: mahabir@mail.nih.gov

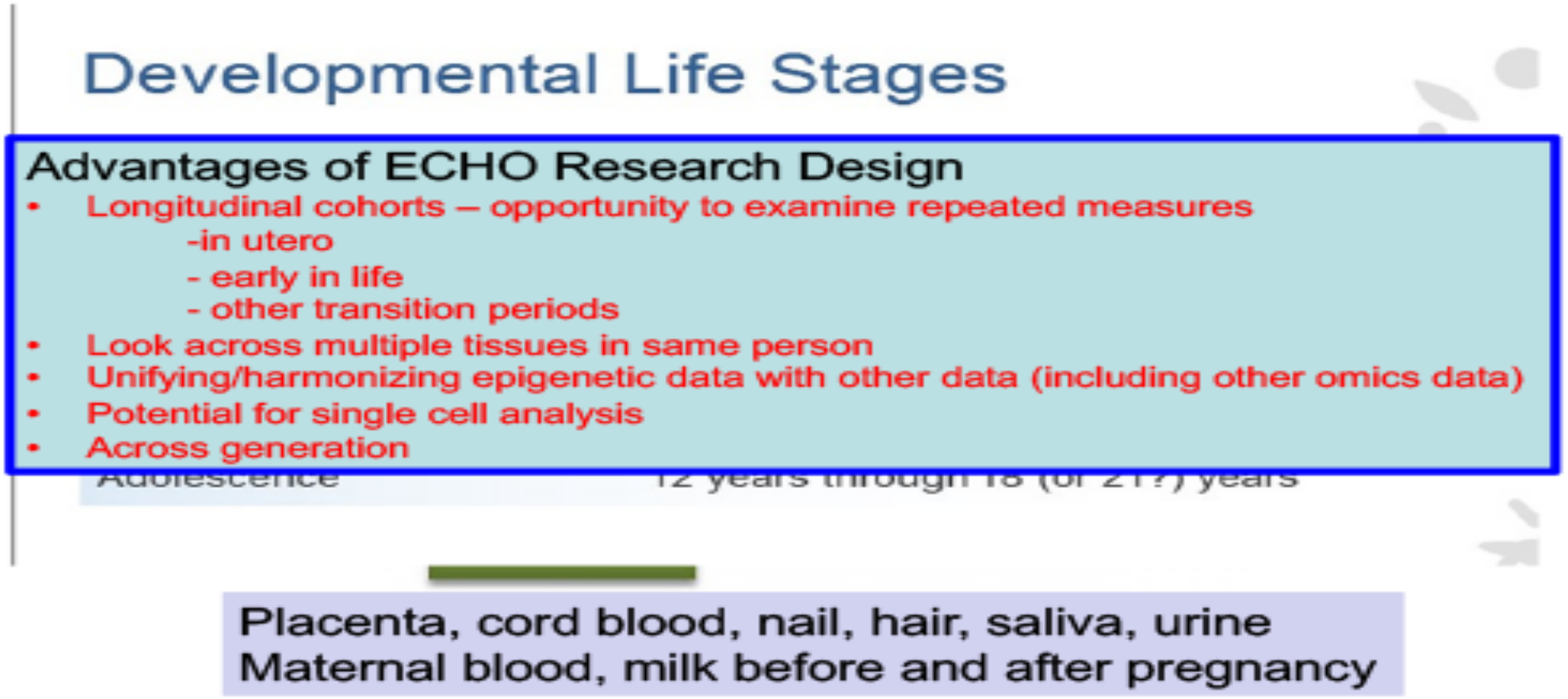
Cancer Med. 2015 Dec;4(12):1908-22

Abstract

There is a growing understanding that several infectious agents are acquired in early life and this is the reason why available vaccines target the new born, infants, and adolescents. Infectious agents are associated with cancer development and it is estimated that about 20% of the world's cancer burden is attributed to infectious agents. There is a growing evidence that certain infectious agents acquired in early life can give rise to cancer development, but estimates of the cancer burden from this early-life acquisition is unknown. In this article, we have selected five cancers (cervical, liver, Burkitt's lymphoma-leukemia, nasopharyngeal carcinoma, and adult T-cell leukemia-lymphoma) and examine their links to infectious agents (HPV, HBV, HCV, EBV, and HTLV-1) acquired in early life. For these agents, the acquisition in early life is from mother-to-child transmission, perinatal contact (with genital tract secretions, amniotic fluids, blood, and breast milk), saliva, sexual intercourse, and blood transfusion. We

Scientific goal

ECHO advantages



Epigenetics and behavior

Epigenetics and behavior (including emotions)

Transl Psychiatry. 2016 Mar 29;6:e765. doi: 10.1038/tp.2016.32.

The effects of maternal anxiety during pregnancy on IGF2/H19 methylation in cord blood.

Mansell T[1,2], Novakovic B[1,2], Meyer B[1,2], Rzehak P[1,3], Vuillermin P[1,2,4,5], Ponsonby AL[1,2], Collier F[4,5], Burgner D[1,2], Saffery R[1,2], Ryan J[1,2,6,7]; BIS investigator team.

Collaborators (11)

Author information

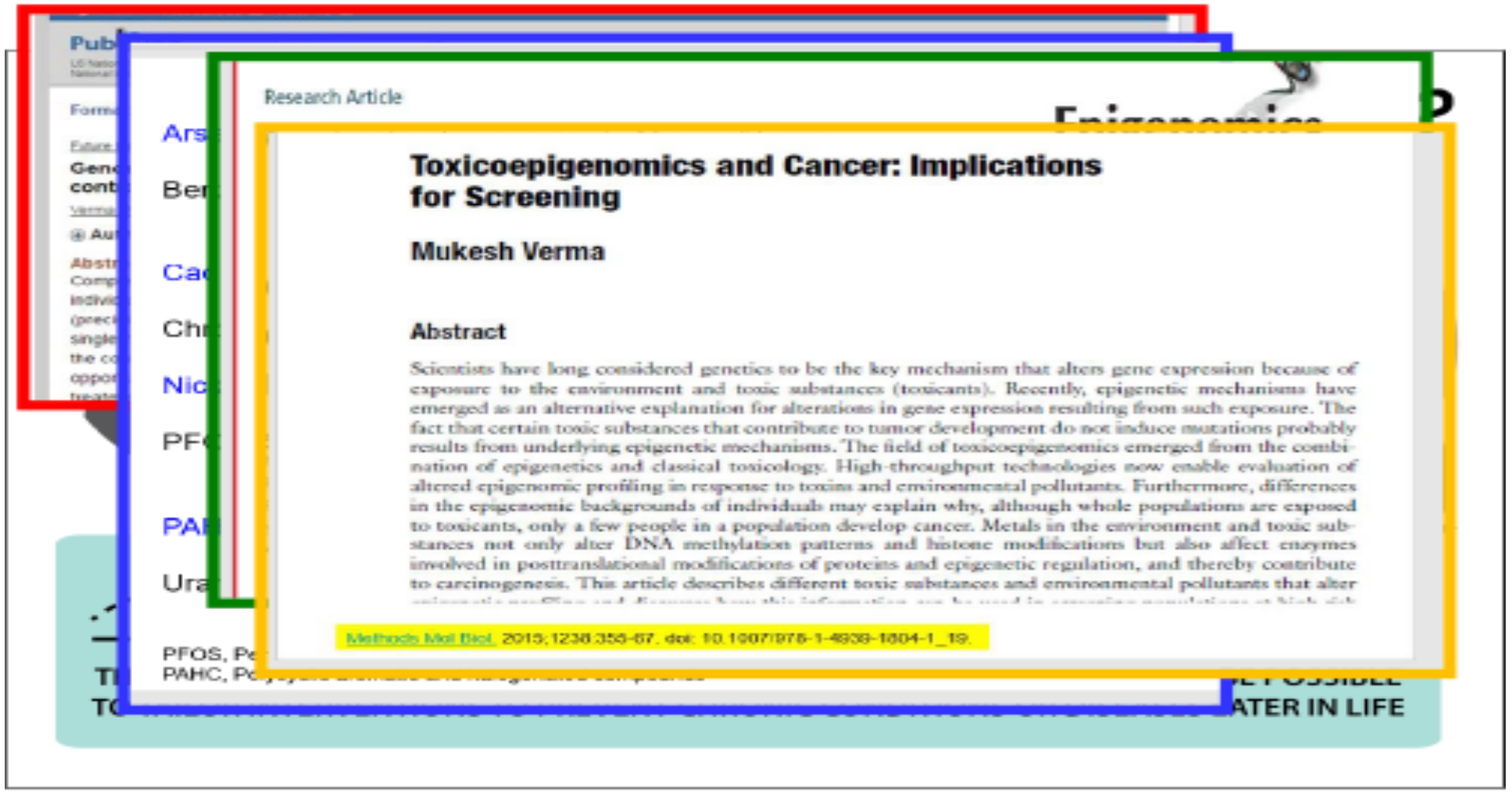
Open/close author information list

Abstract

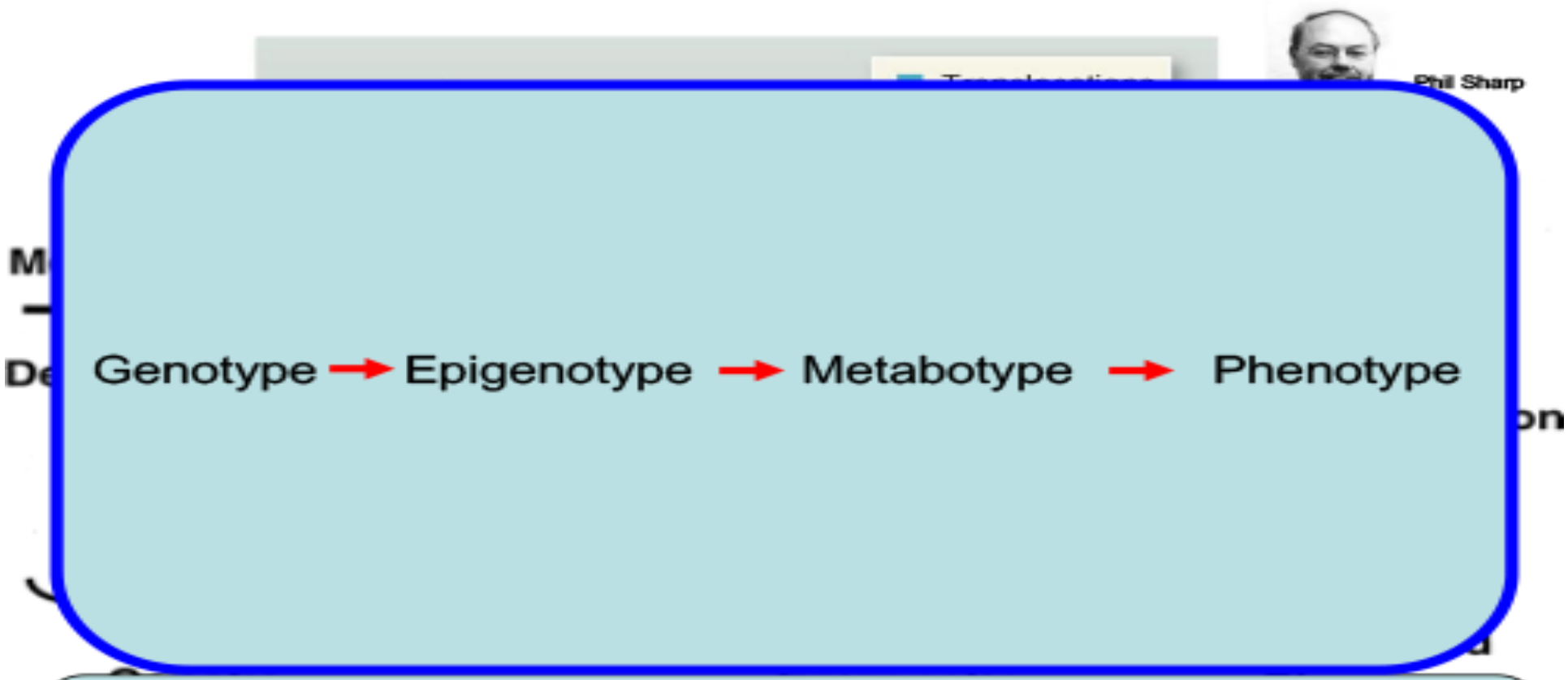
Compelling evidence suggests that maternal mental health in pregnancy can influence fetal development. The imprinted genes, insulin-like growth factor 2 (IGF2) and H19, are involved in fetal growth and each is regulated by DNA methylation. This study aimed to determine the association between maternal mental well-being during pregnancy and differentially methylated regions (DMRs) of IGF2 (DMR0) and the IGF2/H19 imprinting control region (ICR) in newborn offspring. Maternal depression, anxiety and perceived stress were assessed at 28 weeks of pregnancy in the Barwon Infant Study (n=576). DNA methylation was measured in purified cord blood mononuclear cells using the Sequenom

within your DNA that can be controlled by you, by your emotions, beliefs and behavioral choices."

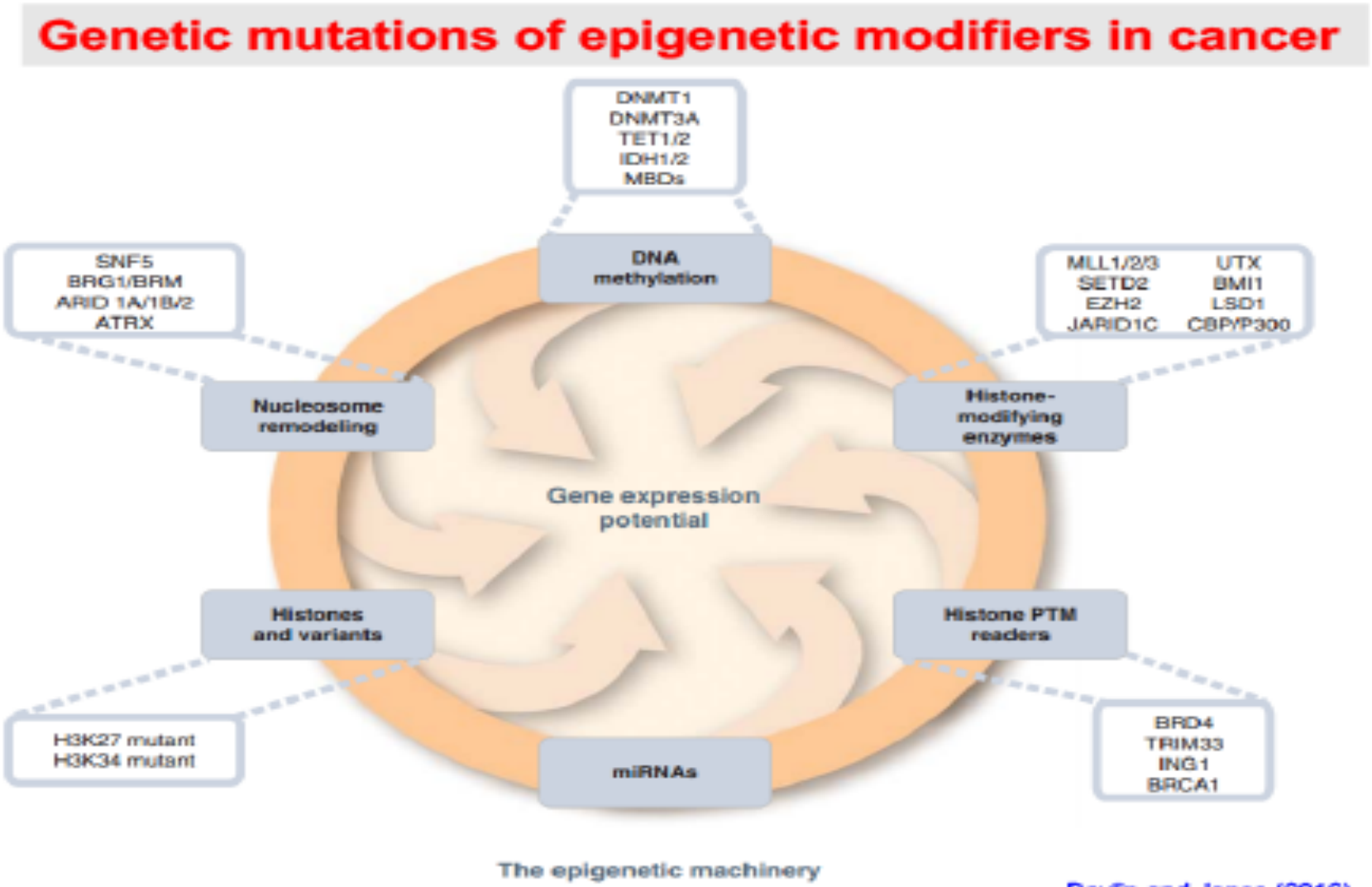
Toxicoepigenomics



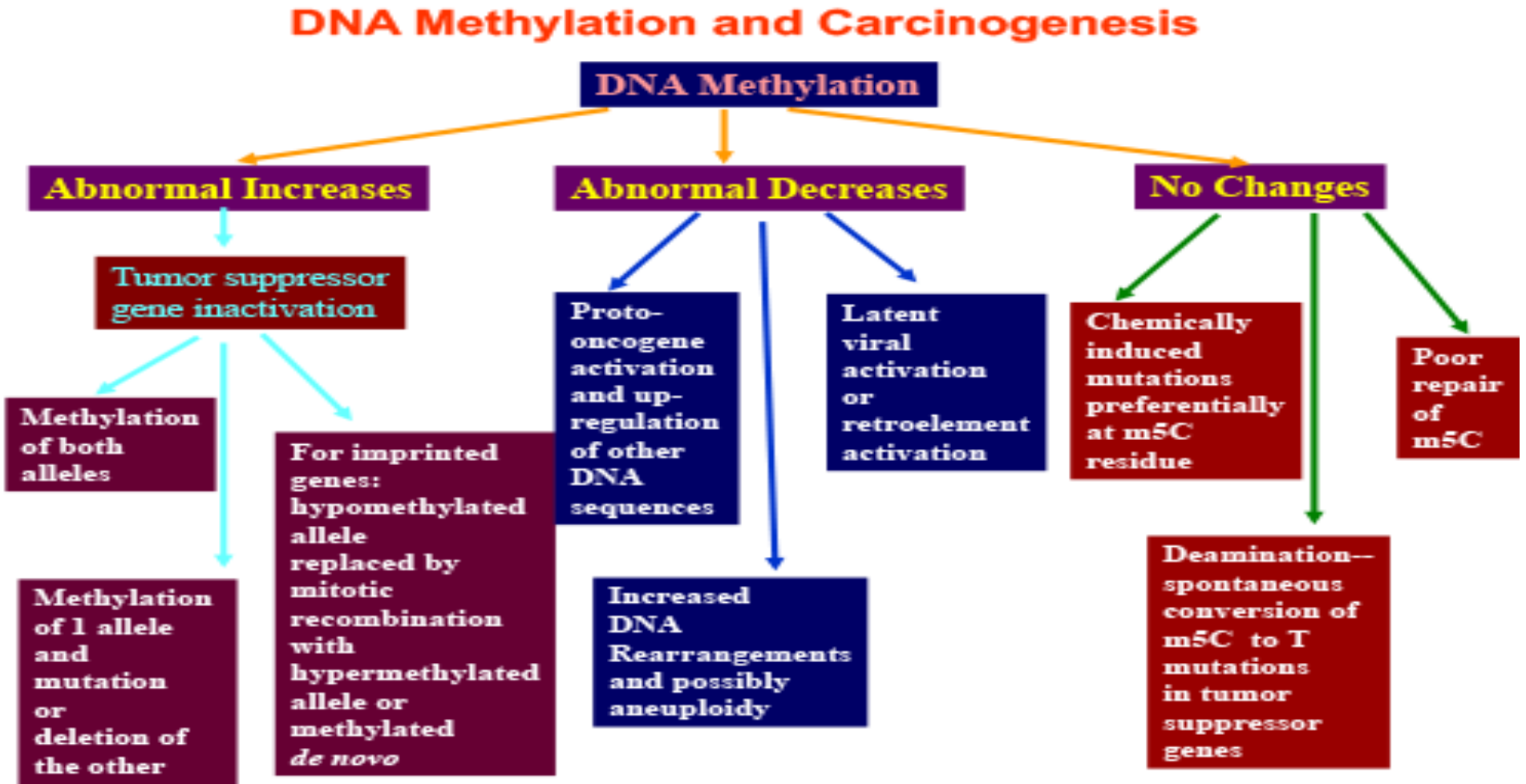
Tumor alterations



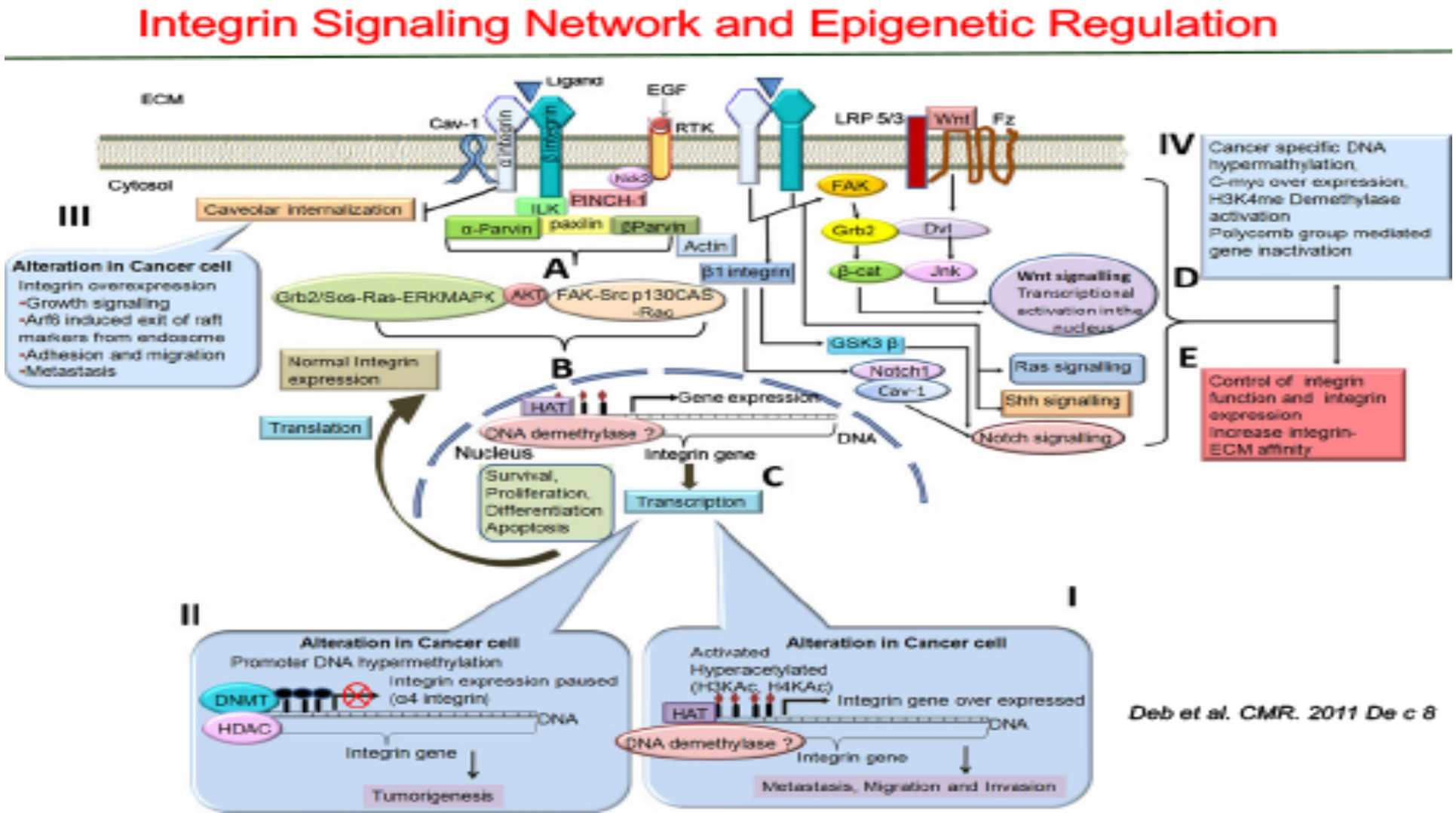
Genetic mutations



DNA methylation and carcinogenesis

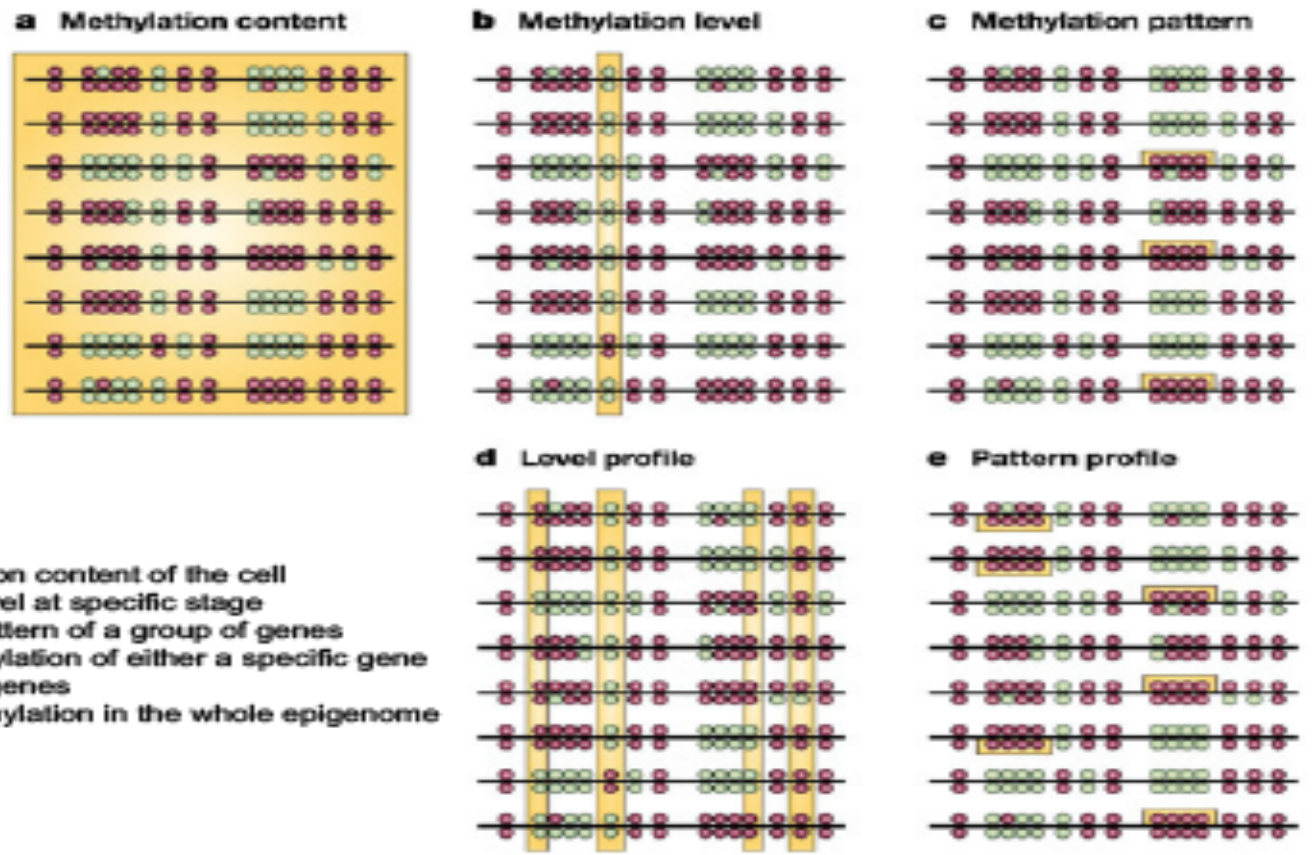


Integrin signaling



Deb et al. CMR. 2011 De c 8

Methylation

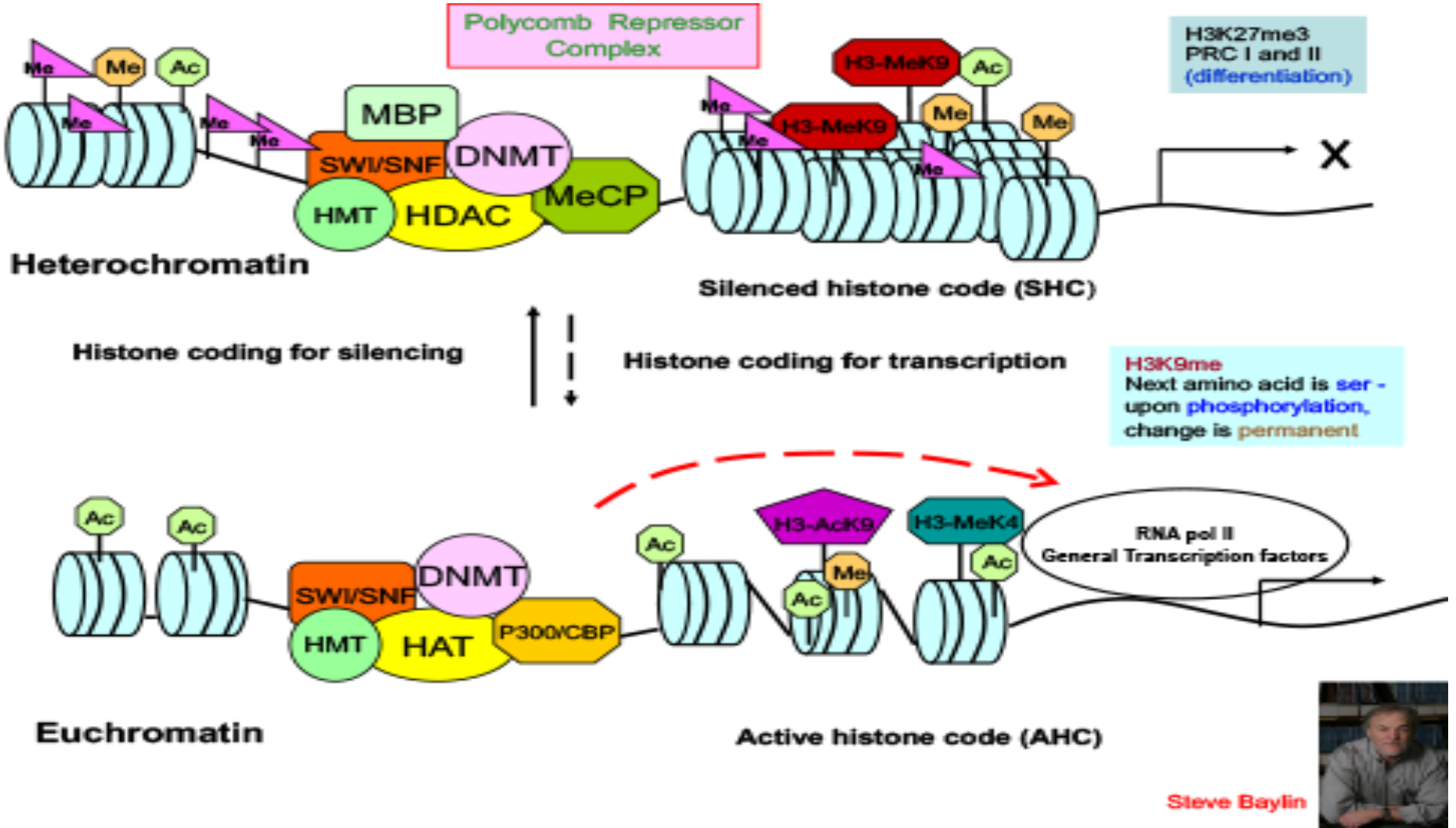


- Total methylation content of the cell
- methylation level at specific stage
- methylation pattern of a group of genes
- profile of methylation of either a specific gene or a number of genes
- pattern of methylation in the whole epigenome

To reduce
- false negative
- false positives

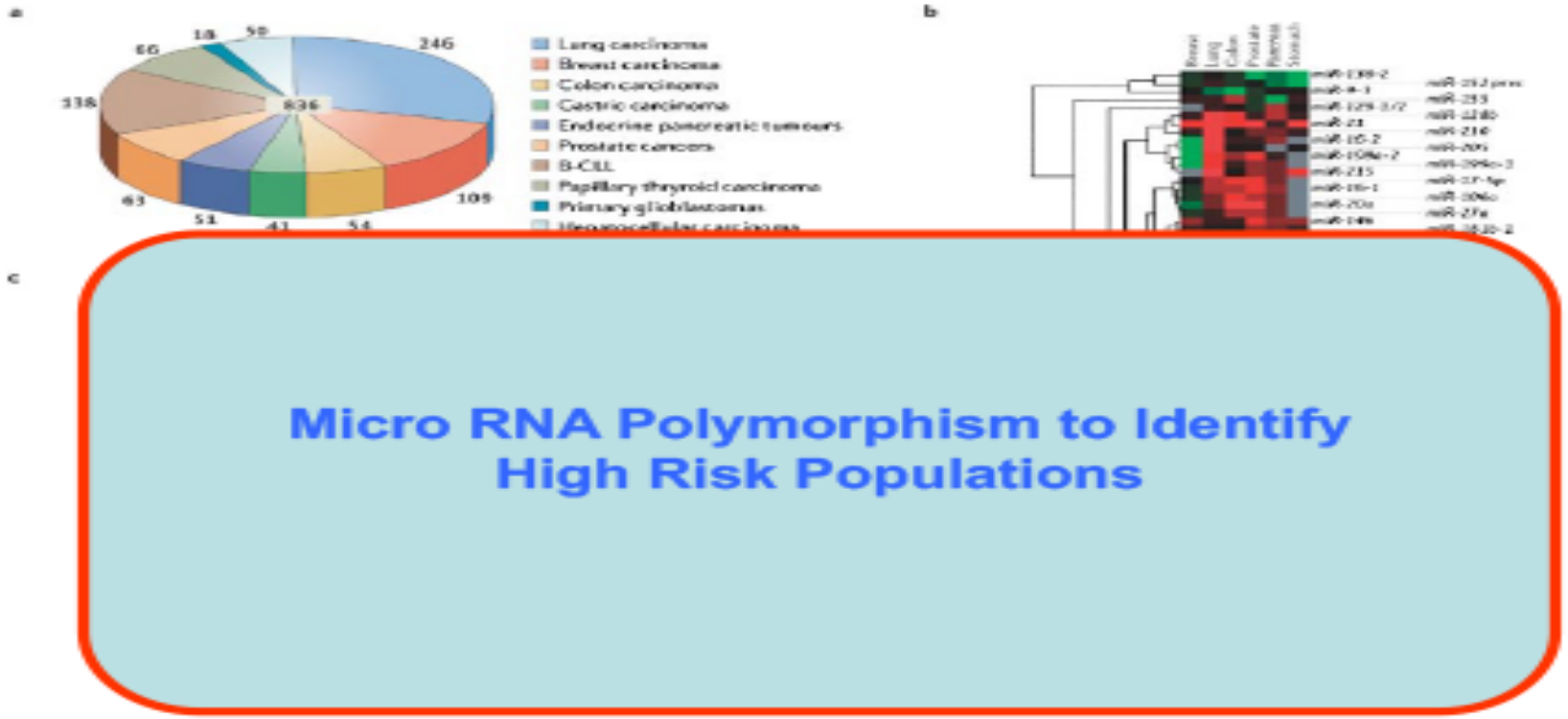
Laird *Nat Rev Cancer* 3:253

Histone acetylation



Micro RNA signatures

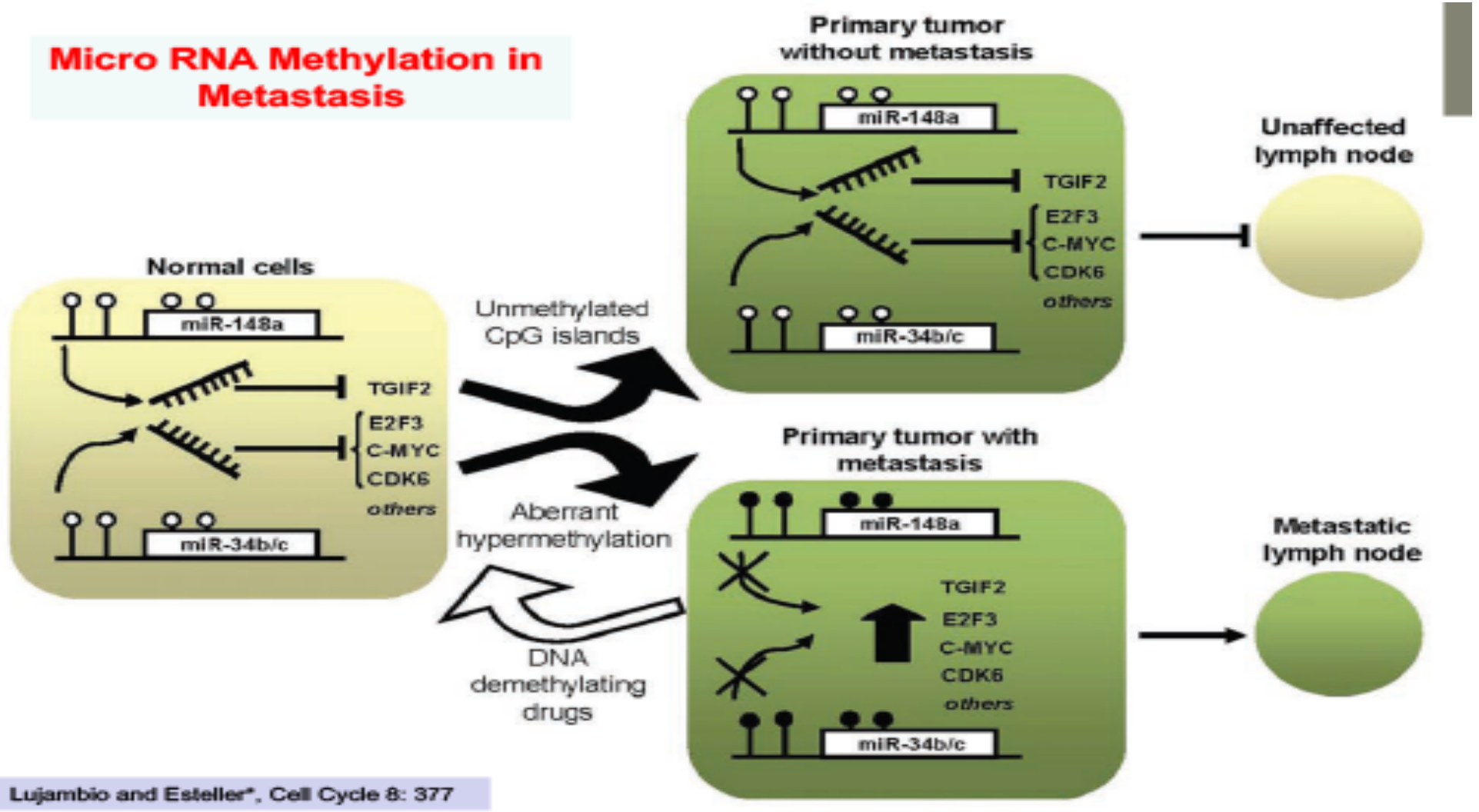
Mirco RNA Signatures in Human Cancers



Mir-31 inhibits metastasis in breast cancer

nature REVIEWS CANCER

Micro RNA methylation



Extracellular vesicles

Verma et al. BMC Clinical Pathology (2015) 15:6
DOI 10.1186/s12907-015-0005-5

BMC
Clinical Pathology

REVIEW Open Access

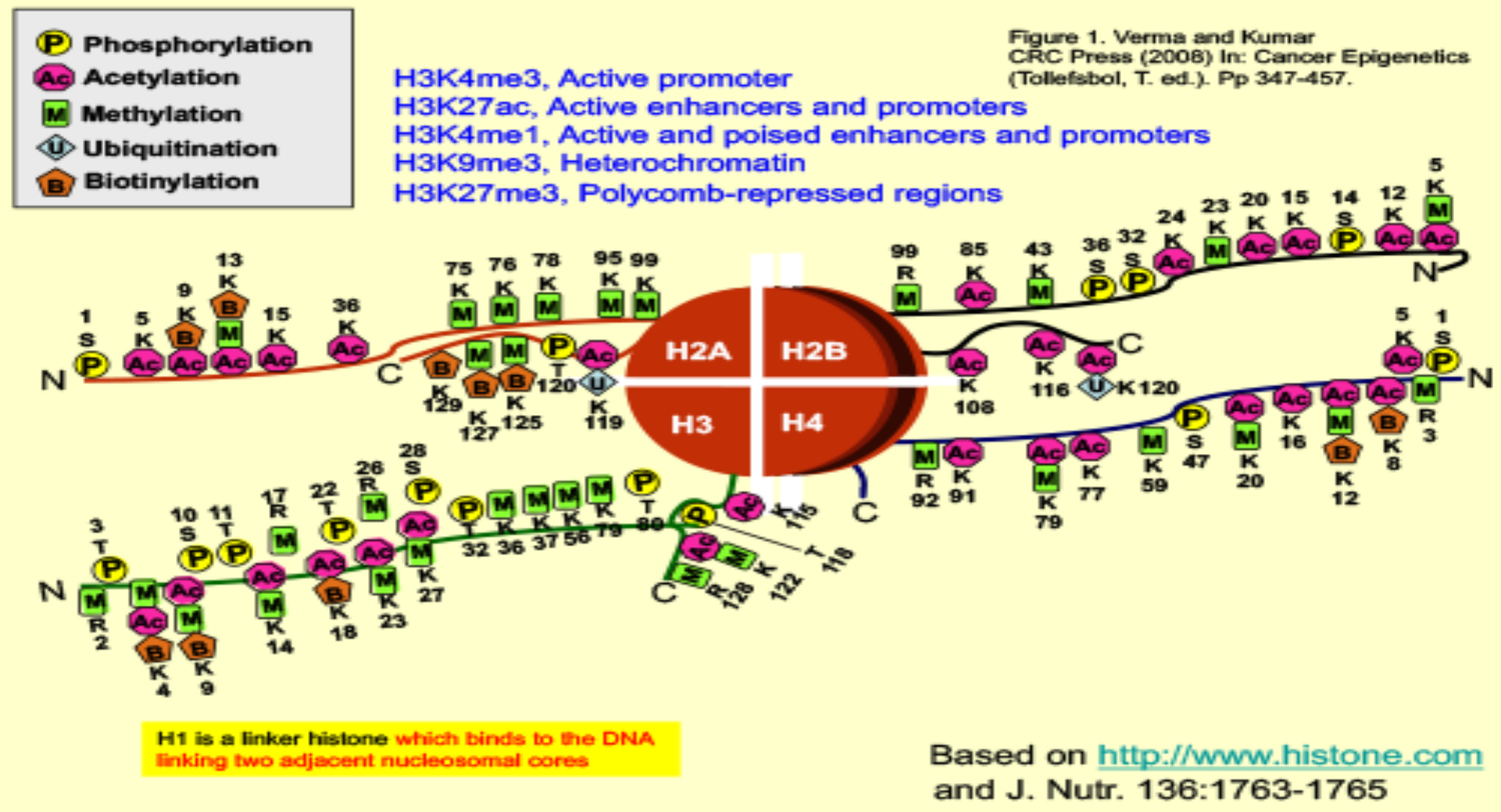
Extracellular vesicles: potential applications in cancer diagnosis, prognosis, and epidemiology

Mukesh Verma*, Tram Kim Lam, Elizabeth Hebert and Rao L Divi

Abstract

Both normal and diseased cells continuously shed extracellular vesicles (EVs) into extracellular space, and the EVs carry molecular signatures and effectors of both health and disease. EVs reflect dynamic changes that are occurring in cells and tissue microenvironment in health and at a different stage of a disease. EVs are capable of altering the function of the recipient cells. Trafficking and reciprocal exchange of molecular information by EVs among different organs and cell types have been shown to contribute to horizontal cellular transformation, cellular reprogramming, functional alterations, and metastasis. EV contents may include tumor suppressors, phosphoproteins, proteases,

Histone modifications



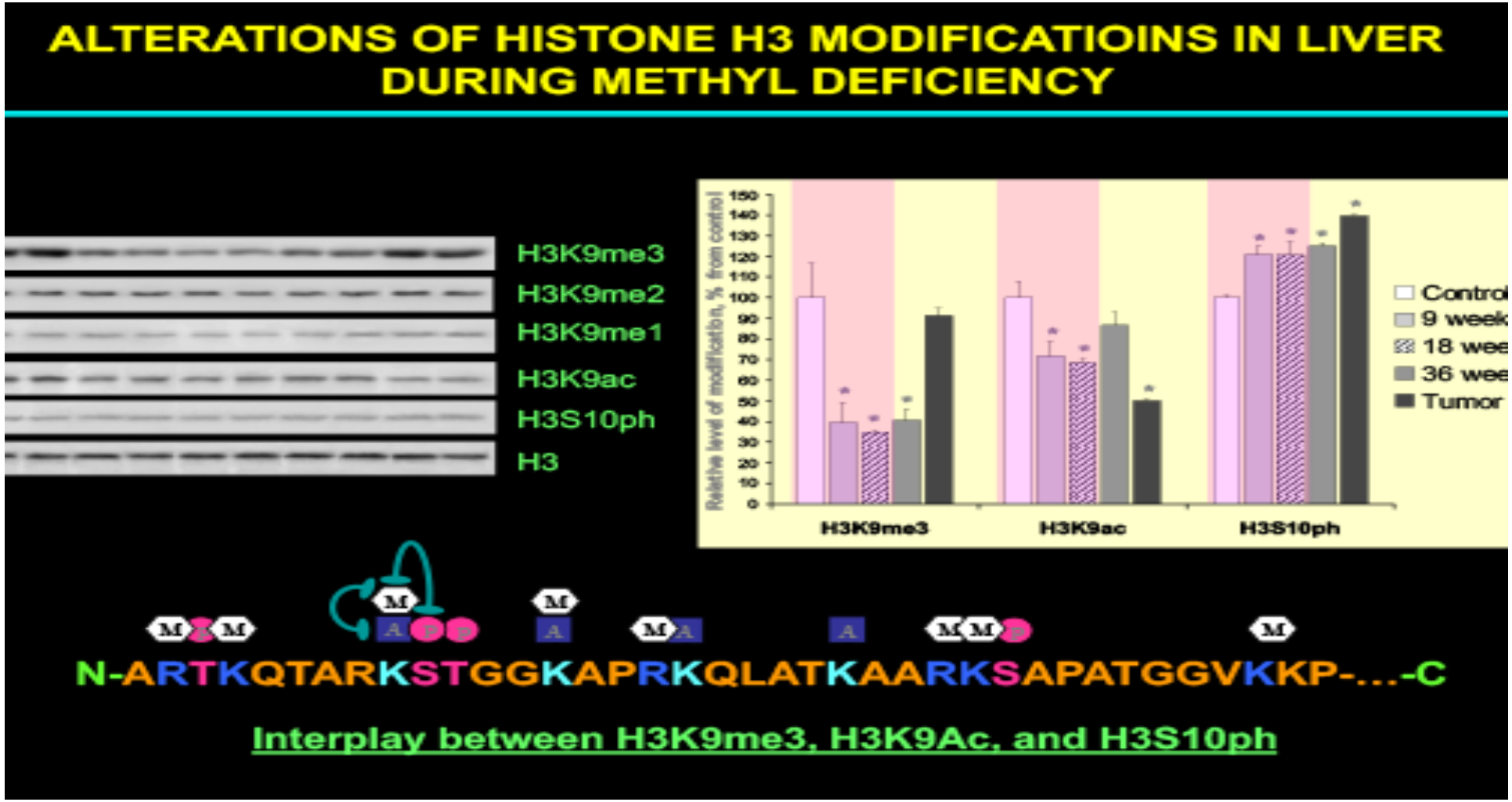
Histones

Clin Epigenetics. 2016; 8: 57

Activating: e.g. H3K4me3

Silencing: e.g. H3K9me3, H3K27me3

Histone H3 modifications



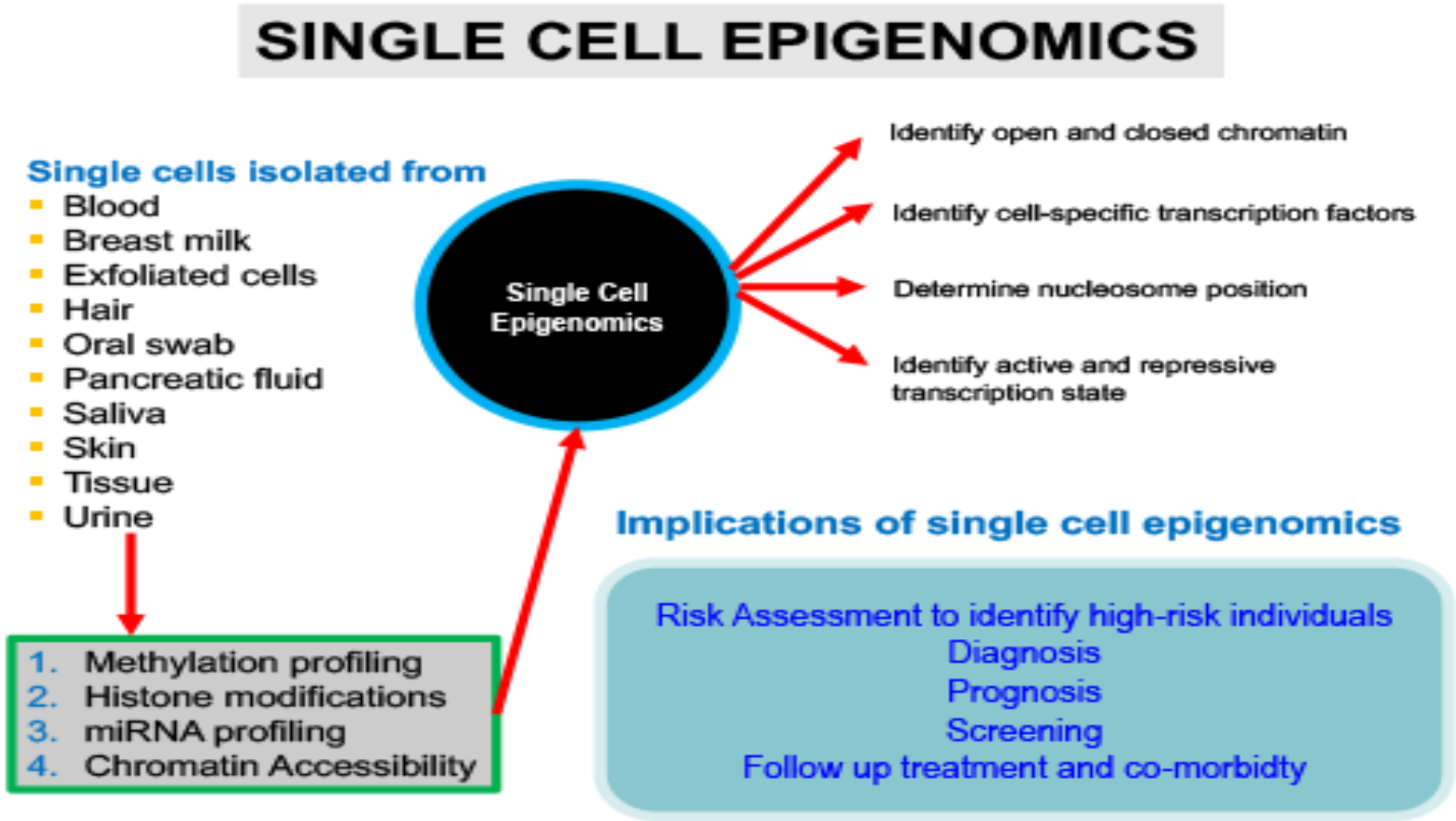
Epigenetic regulation

Epigenetic Gene Regulation:

Modification		Methylation			Acetylation
		Mono-methylation	Di-methylation	Tri-methylation	
DNA		Repression	--	--	--
Histone	H3K4	Activation	Activation	Activation	--
	H3K9	Activation	Repression	Repression	Activation
	H3K27	Activation	Repression	Repression	--
	H3K36	--	Repair	Activation	Activation
	H3K79	Activation	Activation	Activation Repression	--
	H3R17	--	Activation	--	--
	H4K5	--	--	--	Activation
	H4K8	--	--	--	Activation
	H4K12	--	--	--	Activation
	H4K16	--	--	--	Activation
	H4K20	Activation	Activation	Repression	--
	H4K16	--	--	--	Activation

Abnova

Single cell epigenomics



Histone modifications

20 Diagnosing Cancer Using Histone Modification Analysis

Mukesh Verma and Deepak Kumar

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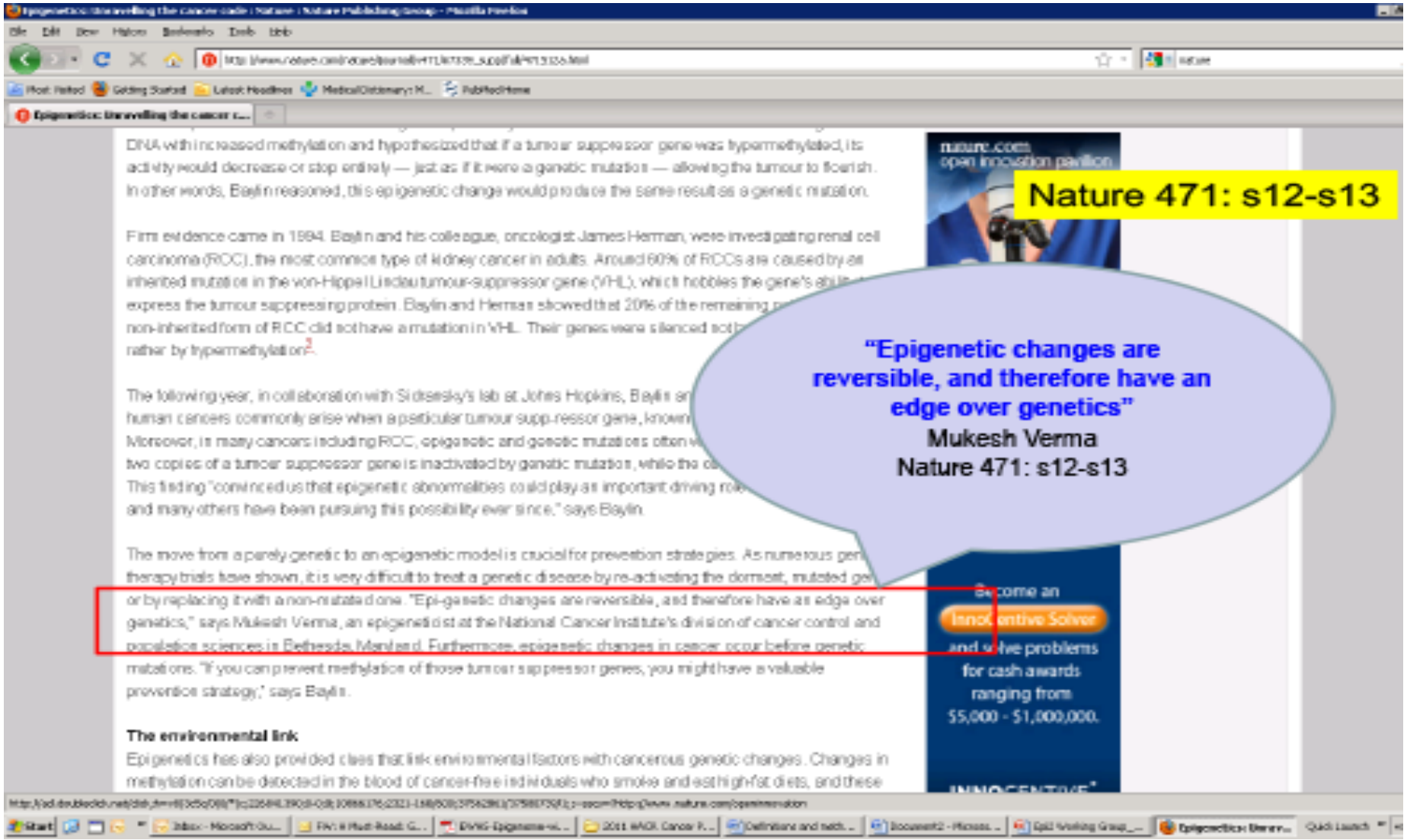
ISBN 9781420045796 - CAT# 45792

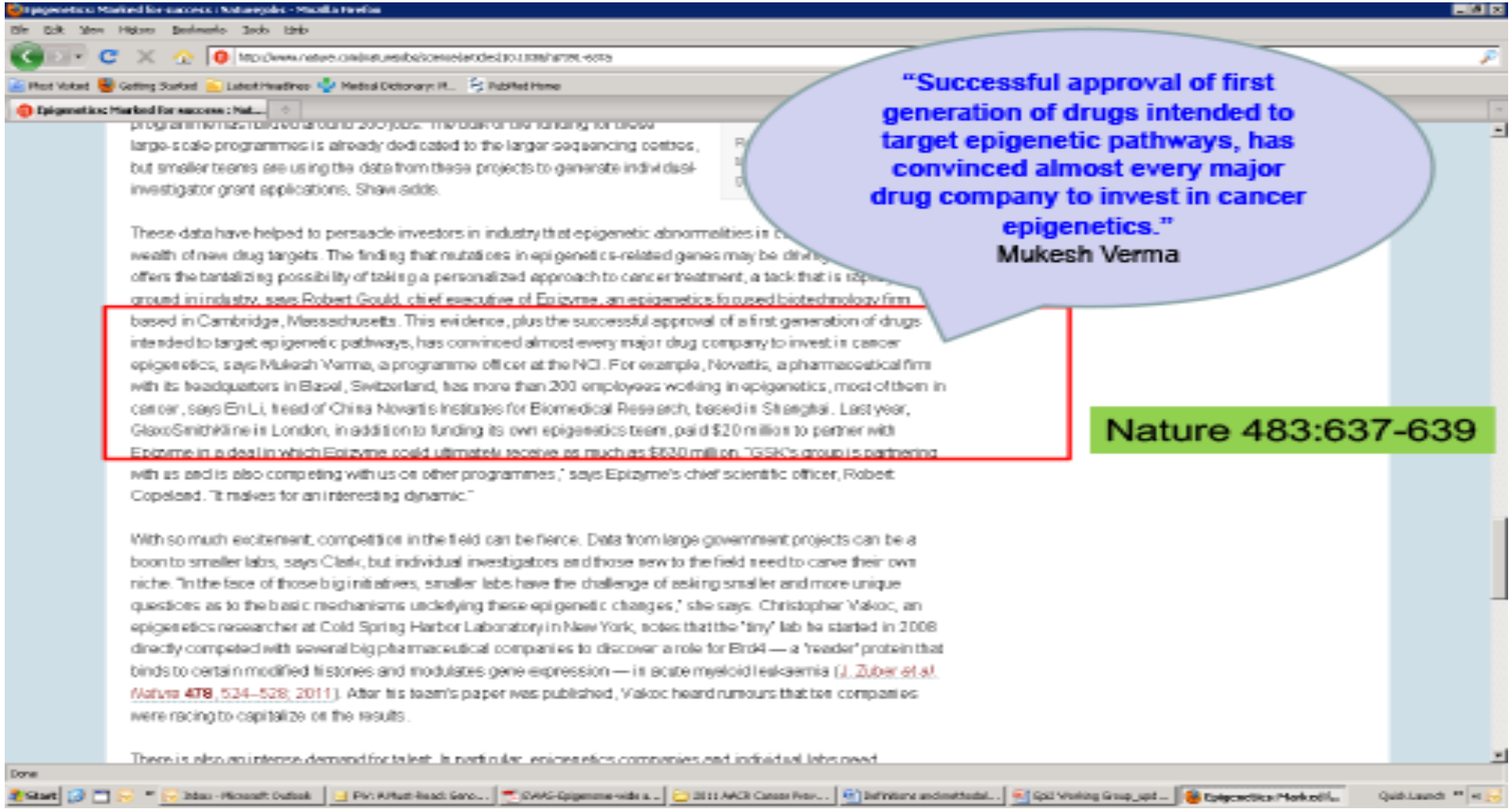
Books

Books edited by Mukesh Verma

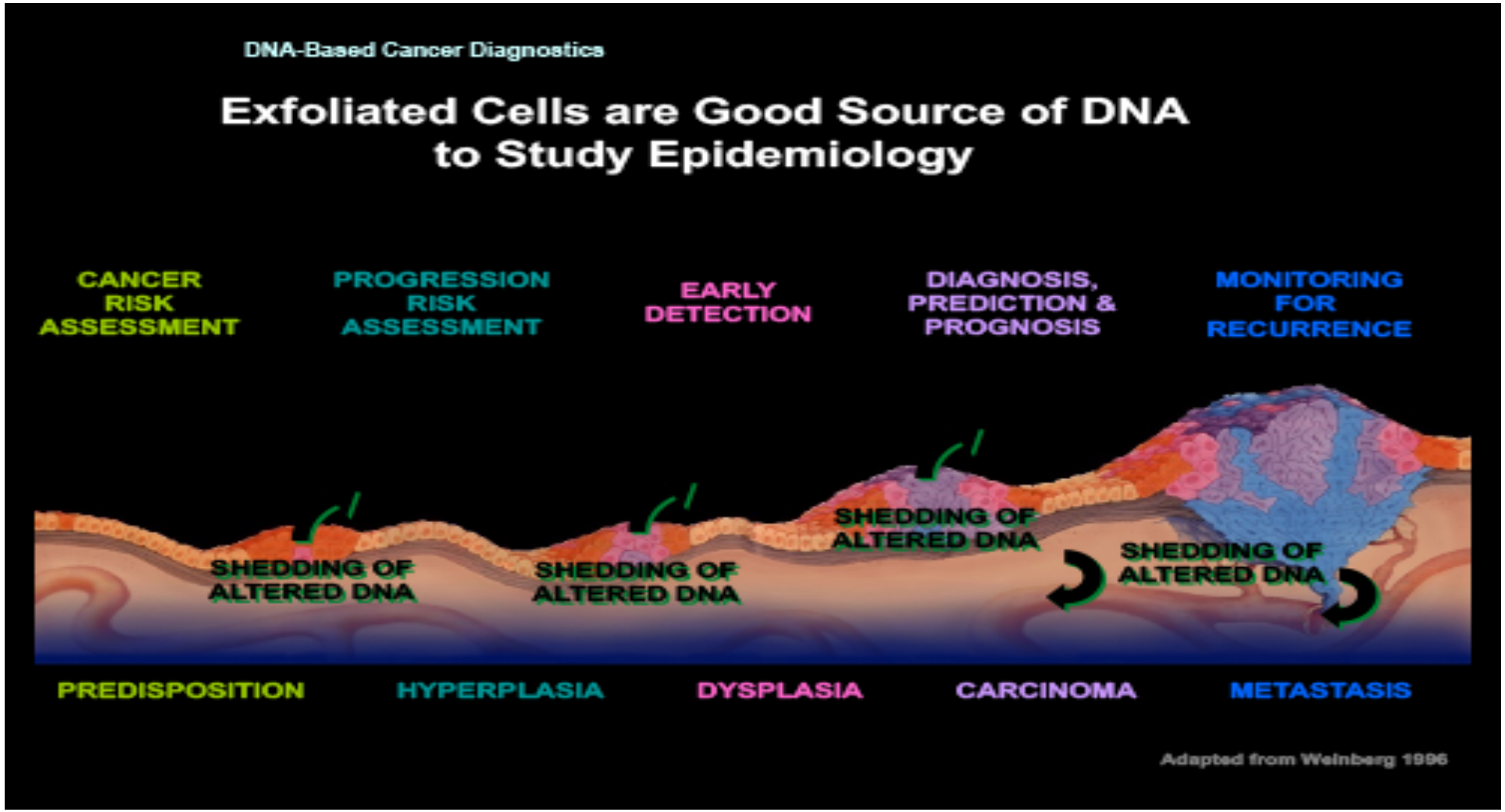
Epigenetic changes



Epigenetic drugs



Exfoliated cells

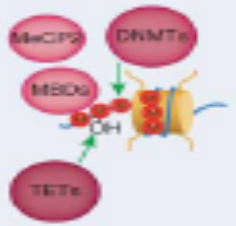


Histone enzymes

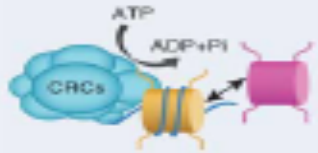
Category	Gene
HDACs	*HDAC1*
	HDAC2
	HDAC6
Sirtuins	*SIRT1*
	SIRT2
	SIRT3
	SIRT7
HDMs	*KDM1A*
	KDM2B
	KDM4C
	KDM5A
	KDM5B
	KDM5C
	KDM6A
	KDM6B

Category	Gene
HATs	*CREBBP*
	EP300
	MYST3
	MYST4
	KAT5
HMTs	*MLL*
	EZH2
	NSD1
	PRDM2
	SMYD3
	WHSC1

Category	Gene
DNMTs	*DNMT1*
	DNMT3A
	DNMT3B
(2OG)-Fe(II)–dependent oxygenases	*TET1*
	TET2
Methyl-CpG binding proteins	*MBD1*
	MBD2
	MBD3
	MBD4
	MECP2



Category	Gene
Histone variants	*H2AFZ*
Chromatin remodeling factors	*ARID1A*
	CHD5
	CHD7
	MTA1
	MTA2
	MTA3
	SMARCA2
	SMARCA4
	SNF5



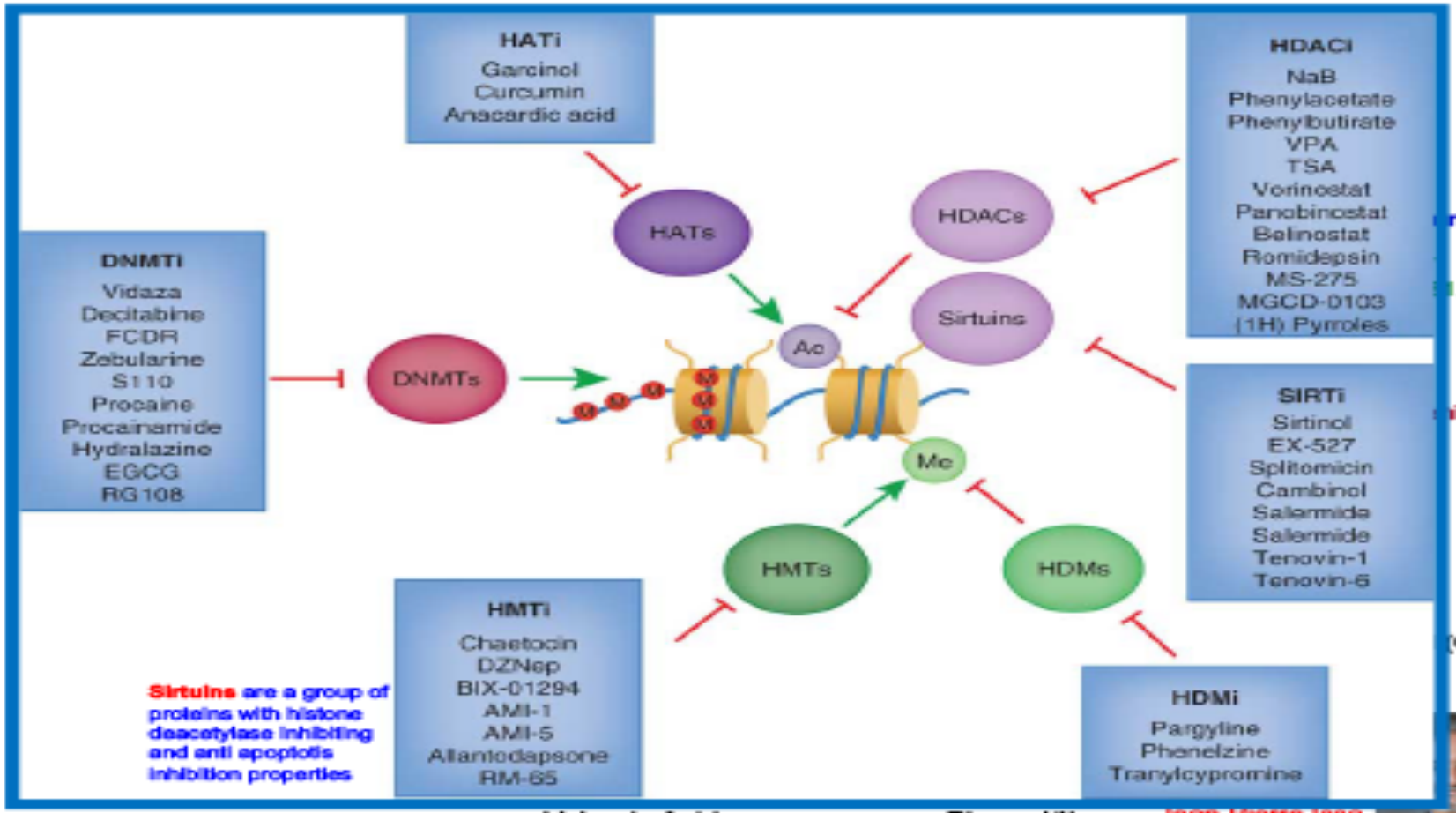
3CACC6

Category	Gene
Histone modification readers	*ING1*
	ING2
	ING3
	ING4
	ING5

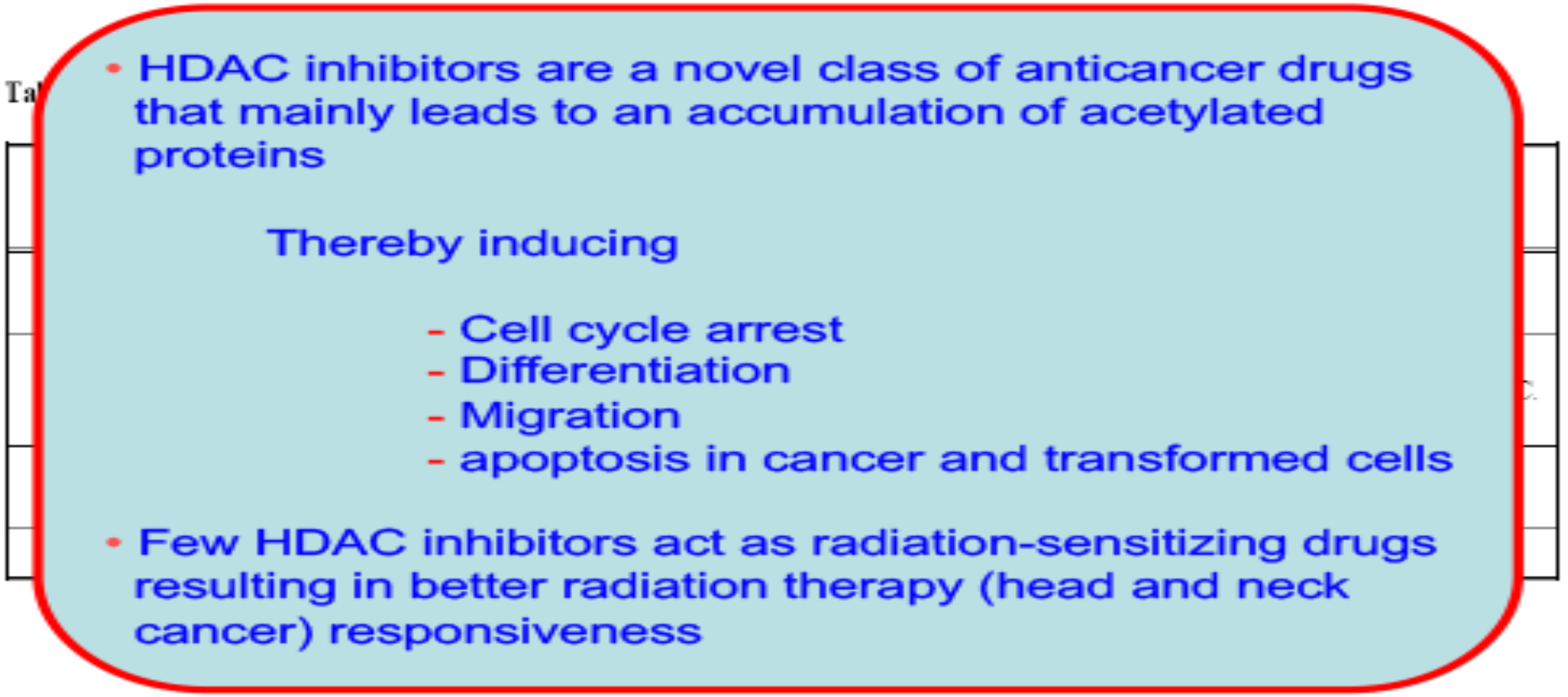
Sirtuins are a group of proteins with histone deacetylase inhibiting and anti apoptotic inhibition properties

Verma and Srivastava (2002). Lancet Oncol. 3: 755-363;
Verma et al (2004) Crit. Rev. Clin. Sc. 41: 585-607;
Verma and Manne (2006). Crit. Rev. Hematol. Oncol. 60: 9-18;
Verma et al (2006). Mol. Diag. Therapy. 10: 1-15.

Methylation and acetylation enzymes



HDAC inhibitors



HDAC 1, 2, 3, 8, 11 have been characterized (Khan, I , 2007)

Phase I study

Phase I study of epigenetic modulation with 5-azacytidine and valproic acid in patients with advanced cancers.

Braiteh F, Soriano AO, Garcia-Manero G, Hong D, Johnson MM, Silva Lde P, Yang H, Alexander S, Wolff J, Kurzrock R. Clin Cancer Res.14(19):6296-301. (colorectal cancer, melanoma and breast cancer)

5 Azacytidine
S.C. daily for 10 days

+

Valproic Acid
Orally daily to titrate to 75-100 ug/ml

28 Days Cycle

55 people with Advanced cancer Median age 60

Peripheral blood
- Pyrosequencing
- Chip

Analysis Day 1, 10 and 28

- **The maximum tolerated dose was 75 mg/m(2) of 5-AZA in combination with valproic acid.**
- **Dose-limiting toxicities were neutropenic fever and thrombocytopenia, which occurred at a dose of 94 mg/m(2) of 5-AZA.**
- **Stable disease lasting 4 to 12 months (median, 6 months) was observed in 14 patients (25%).**

A significant decrease in global DNA methylation and induction of histone acetylation were observed.

The combination of 5-AZA and valproic acid is safe at doses up to 75 mg/m(2) for 5-AZA in patients with advanced malignancies.

5-azacytidine, valproic acid and ATRA

Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome.

Soriano et al. Blood. 110(7):2302-8.

- **Combination of 5-azacitidine (5-AZA), valproic acid (VPA), and ATRA in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome.**
- **A total of 53 patients were treated.**
- **The overall response rate was 42%.**
- **A significant decrease in global DNA methylation and induction of histone acetylation were achieved.**
- **VPA blood levels were higher in responders.**
- **The combination studied is safe and has significant clinical activity.**

This clinical trial was registered at www.clinicaltrials.gov as no. NCT00326170.

Histone inhibitors

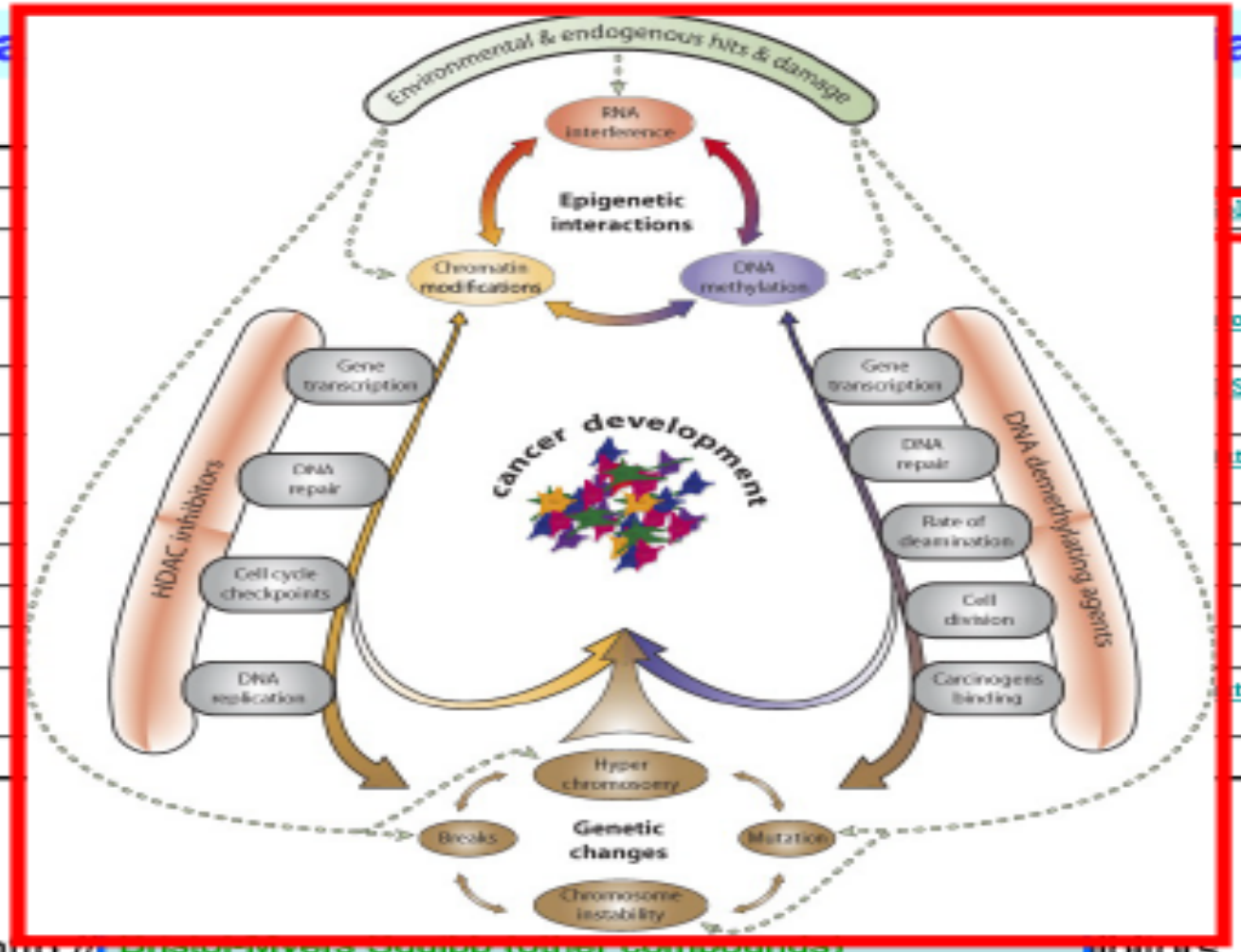
Histone Inhibitors in Clinical Trials (Clinicaltrials.gov)

STATUS	STUDY
Recruiting	Safety Study of the Histone Deacetylase Inhibitor, CHR-3996, in Patients With Advanced Solid Tumours
Recruiting	Phase II Study of Histone-Deacetylase Inhibitor ITF2357 in Refractory/Relapsed Lymphocytic Leukemia
Recruiting	phII Study of an HDAC Inhibitor in Very High-Risk Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	Phase IIA Study of the HDAC Inhibitor ITF2357 in Patients With JAK-2 V617F Positive Chronic Myeloproliferative Diseases
Recruiting	Phase II Trial of the Histone-Deacetylase Inhibitor ITF2357 Followed by Mechlorethamine in Relapsed/Refractory Hodgkin's Lymphoma Patients
Recruiting	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer
Recruiting	Valproic Acid, Temozolomide, and Radiation Therapy in Treating Patients With Glioblastoma Multiforme
Recruiting	Study of Vorinostat (MK0683) an HDAC Inhibitor, or Placebo in Combination With Bortezomib in Patients With Multiple Myeloma
Recruiting	Study of Vorinostat (MK0683), an HDAC Inhibitor, in Combination With Bortezomib in Patients With Relapsed or Refractory Multiple Myeloma
Completed	A Phase II Study of Epigenetic Therapy to Overcome Chemotherapy Resistance in Refractory Solid Tumors
Recruiting	Sorafenib and LBH589 in Hepatocellular Carcinoma (HCC)
Recriting	Phase II Study of Valproic Acid With FEC100 for Patients With Locally Advanced Breast Cancer

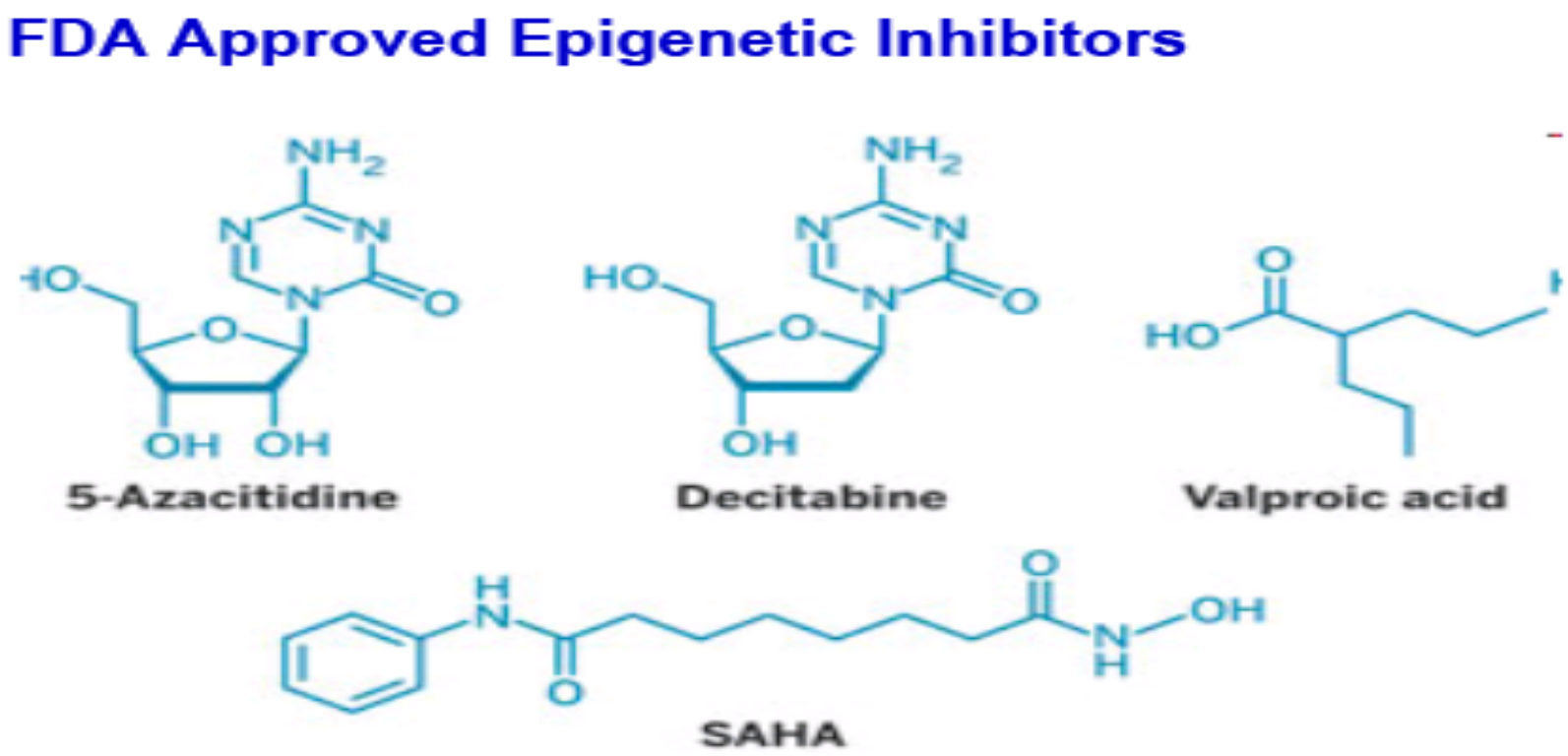
Total : 84 studies

http://clinicaltrials.gov/ct2/results?term=histone+inhibitors&pg=4

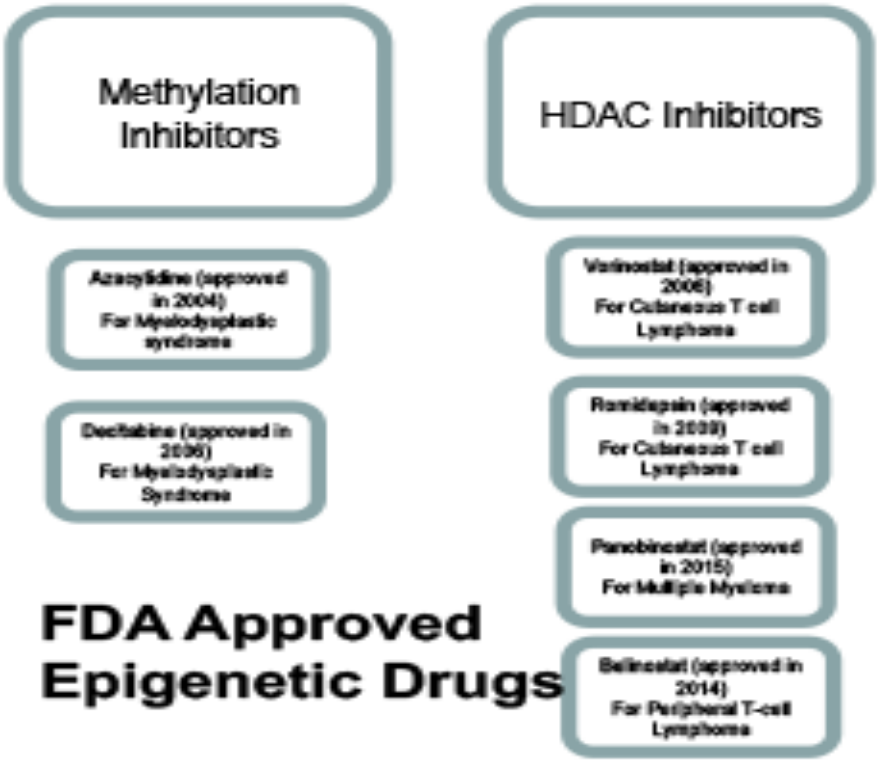
Environmental damage



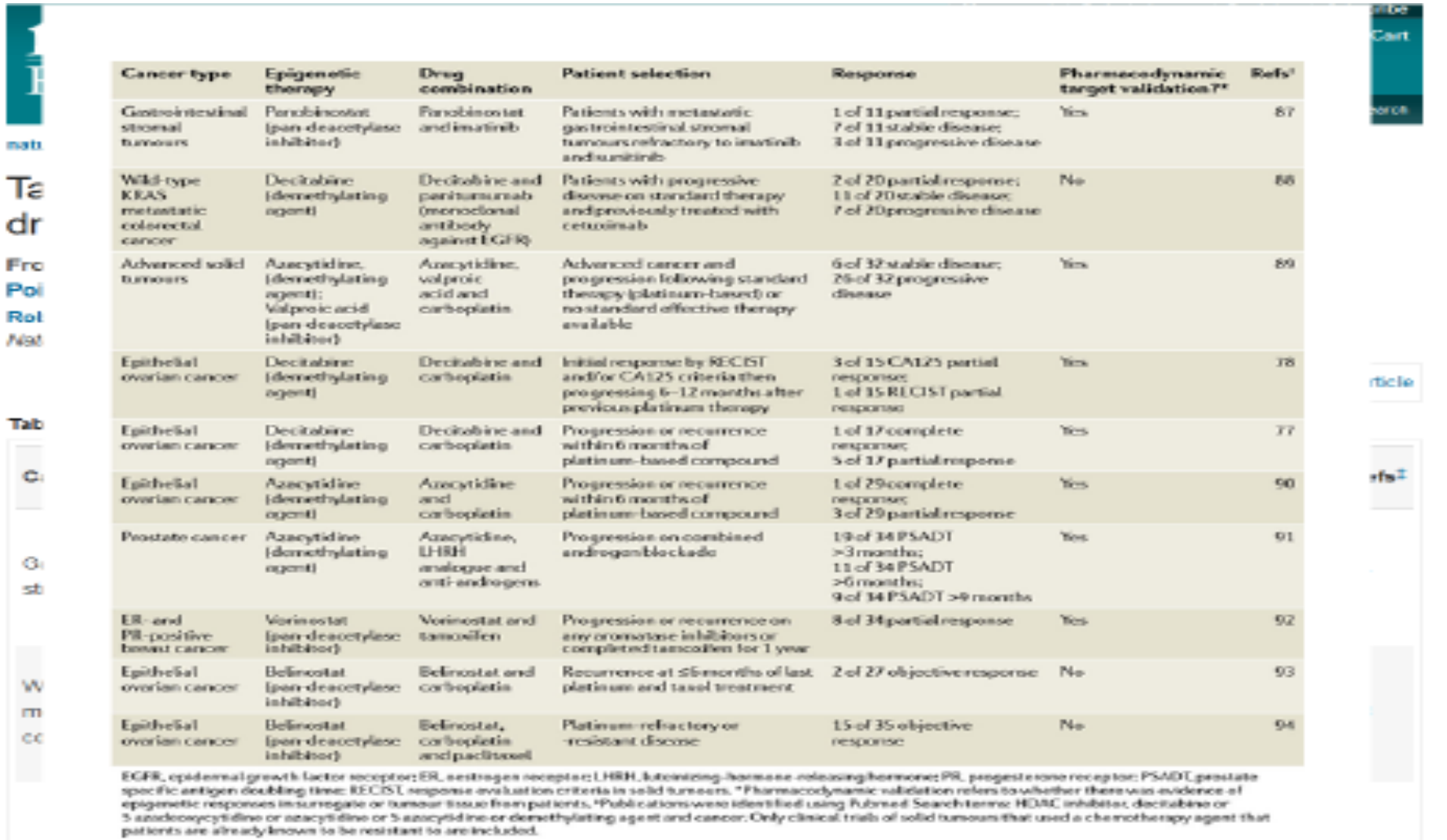
Epigenetic inhibitors



Approved epigenetic drugs



Epigenetic drugs



Cancer type	Epigenetic therapy	Drug combination	Patient selection	Response	Pharmacodynamic target validation?*	Refs‡
Gastrointestinal stromal tumours	Panobinostat (pan-deacetylase inhibitor)	Panobinostat and imatinib	Patients with metastatic gastrointestinal stromal tumours refractory to imatinib and sunitinib	1 of 11 partial response; 7 of 11 stable disease; 3 of 11 progressive disease	Yes	87
Wild-type KRAS metastatic colorectal cancer	Decitabine (demethylating agent)	Decitabine and panitumumab (monoclonal antibody against EGFR)	Patients with progressive disease on standard therapy and previously treated with cetuximab	2 of 20 partial response; 11 of 20 stable disease; 7 of 20 progressive disease	No	88
Advanced solid tumours	Azacytidine (demethylating agent); Valproic acid (pan-deacetylase inhibitor)	Azacytidine, valproic acid and carboplatin	Advanced cancer and progression following standard therapy (platinum-based) or no standard effective therapy available	6 of 32 stable disease; 26 of 32 progressive disease	Yes	89
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Initial response by RECIST and/or CA125 criteria then progressing 6–12 months after previous platinum therapy	3 of 15 CA125 partial response; 1 of 15 RECIST partial response	Yes	78
Epithelial ovarian cancer	Decitabine (demethylating agent)	Decitabine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 17 complete response; 5 of 17 partial response	Yes	77
Epithelial ovarian cancer	Azacytidine (demethylating agent)	Azacytidine and carboplatin	Progression or recurrence within 6 months of platinum-based compound	1 of 29 complete response; 3 of 29 partial response	Yes	90
Prostate cancer	Azacytidine (demethylating agent)	Azacytidine, LHRH analogue and anti-androgens	Progression on combined androgen blockade	19 of 34 PSADT >3 months; 11 of 34 PSADT >6 months; 9 of 34 PSADT >9 months	Yes	91
ER- and PR-positive breast cancer	Vorinostat (pan-deacetylase inhibitor)	Vorinostat and tamoxifen	Progression or recurrence on any aromatase inhibitors or completed tamoxifen for 1 year	8 of 34 partial response	Yes	92
Epithelial ovarian cancer	Belinostat (pan-deacetylase inhibitor)	Belinostat and carboplatin	Recurrence at ≤6 months of last platinum and taxol treatment	2 of 27 objective response	No	93
Epithelial ovarian cancer	Belinostat (pan-deacetylase inhibitor)	Belinostat, carboplatin and paclitaxel	Platinum-refractory or -resistant disease	15 of 35 objective response	No	94

EGFR, epidermal growth factor receptor; ER, oestrogen receptor; LHRH, luteinizing-hormone-releasing hormone; PR, progesterone receptor; PSADT, prostate specific antigen doubling time; RECIST, response evaluation criteria in solid tumours. *Pharmacodynamic validation refers to whether there was evidence of epigenetic responses in surrogate or tumour tissue from patients. ‡Publications were identified using Pubmed Search terms: HDAC inhibitor, decitabine or 5 azadeoxycytidine or azacytidine or 5 azacytidine or demethylating agent and cancer. Only clinical trials of solid tumours that used a chemotherapy agent that patients are already known to be resistant to are included.

Combination therapy

AML subtypes and combination therapy

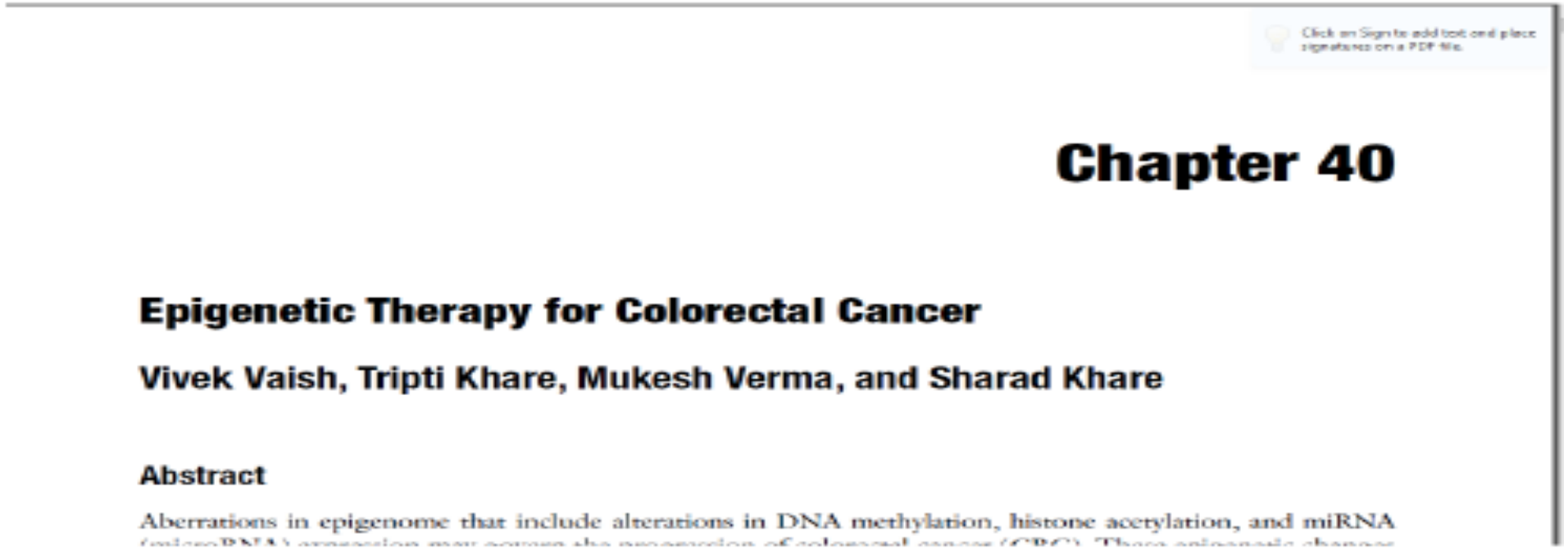
Pharmaceutical Participation

AML Subtype	Drug	Company
Tet2/WTI	CD33 + Aza	BI
IDH2 Mutation	Enasidenib	Celgene
MLL	Entospletinib (Syk inhibitor)	Gilead
CBF	Samalizumab (CD200 Ab) + induction	Alexion
P53 mutation	Entospletinib (Syk inhibitor) + Decitabine	Gilead
Complex Karotype	Entospletinib (Syk inhibitor) + Decitabine	Gilead
P53 mutation	Pevonedistat (Nedd8 inhibitor) + Aza	Takeda
Marker Negative	CD33 + Aza	BI
NPM1 w FLT3 WT	Entospletinib (Syk inhibitor)	Gilead
FLT3 mutation	Gilteritinib	Astellas
IDH1 Mutation	Ivosidenib + Aza	Agios

Source: Leukemia & Lymphoma Society

Cancer letters 17 July 2018

Epigenetic therapy



Click on Sign to add text and place signatures on a PDF file.

Chapter 40

Epigenetic Therapy for Colorectal Cancer

Vivek Vaish, Tripti Khare, Mukesh Verma, and Sharad Khare

Abstract

Aberrations in epigenome that include alterations in DNA methylation, histone acetylation, and miRNA

Methods Mol Biol. 2015;1238:771-82. doi: 10.1007/978-1-4939-1804-1_40

Combination epigenetic therapy

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National Institutes of Health

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Cancer Discov. 2011 Dec;1(7):598-607. doi: 10.1158/2159-8290.CD-11-0214. Epub 2011 Nov 9.

Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer.

Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgado IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM.

Department of Oncology, Johns Hopkins University, Baltimore, Maryland 21231, USA.

Abstract

Epigenetic alterations are strongly associated with the development of cancer. We conducted a phase III trial of combined epigenetic therapy with azacitidine and entinostat, inhibitors of DNA methylation and histone deacetylation, respectively, in extensively pretreated patients with recurrent metastatic non-small cell lung cancer. This therapy is well tolerated, and objective responses were observed, including a complete response and a partial response in a patient who remains alive and without disease progression approximately 2 years after completing protocol therapy. Median survival in the entire cohort was 6.4 months (95% CI 3.8–9.2), comparing favorably with existing therapeutic options. Demethylation of a set of 4 epigenetically silenced genes known to be associated with lung cancer was detectable in serial blood samples in these patients and was associated with improved progression-free ($P = 0.034$) and overall survival ($P = 0.035$). Four of 19 patients had major objective responses to subsequent anticancer therapies given immediately after epigenetic therapy. Significance: This study demonstrates that combined epigenetic therapy with low-dose azacitidine and entinostat results in objective, durable responses in patients with solid tumors and defines a blood-based biomarker that correlates with clinical benefit.

Comment in

A combined epigenetic therapy equals the efficacy of conventional chemotherapy in refractory advanced non-small cell lung cancer. [Cancer Discov. 2011]

PMID: 22585882 [PubMed - indexed for MEDLINE] PMCID: PMC3353724 [Available on 2012/12/1]

Publication Types, MeSH Terms, Substances, Grant Support

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Randomized pha
without entinostat

Combination ther
suppresses tumo

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circulating DNA

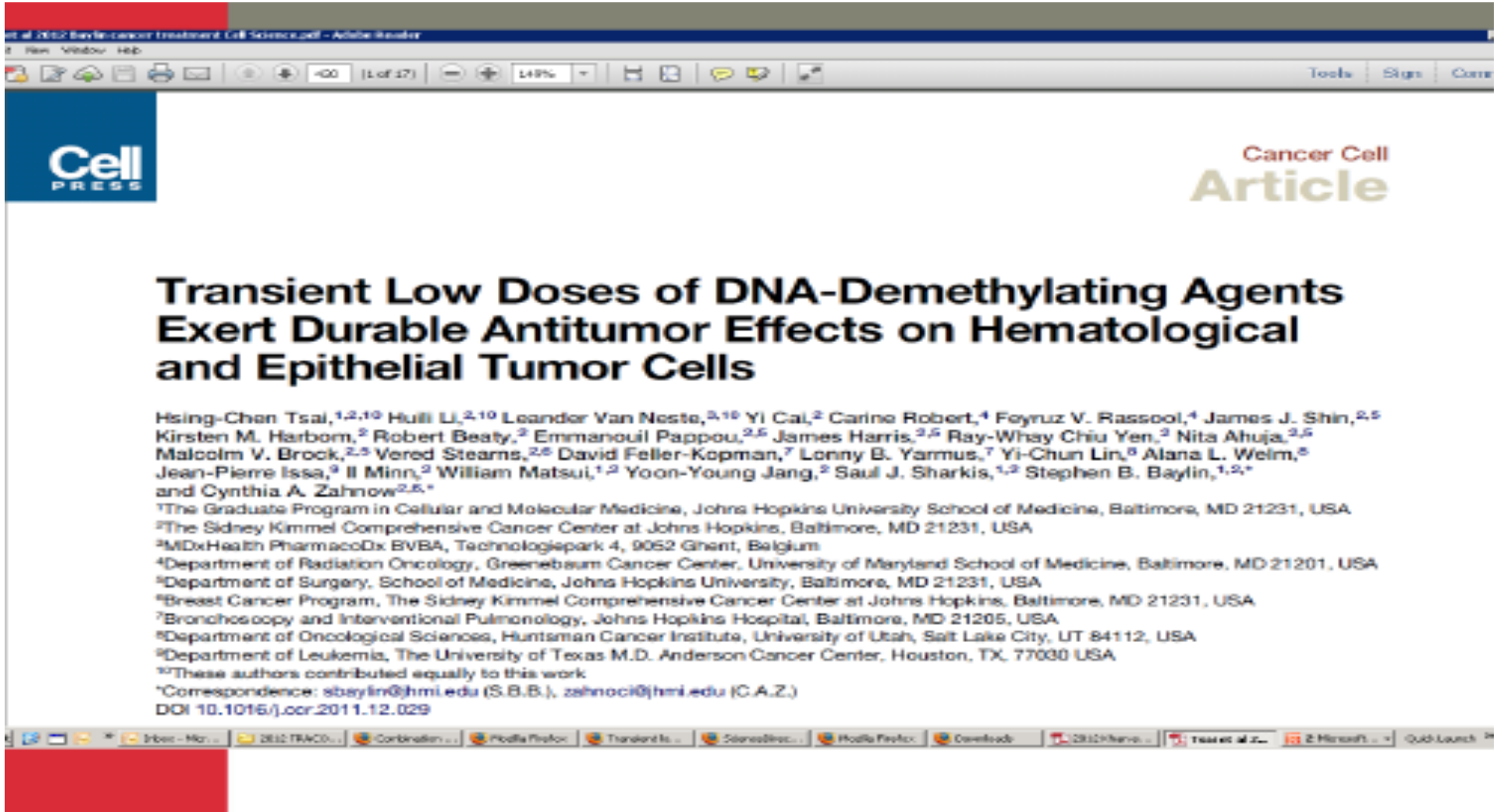
Review Gefitinib
cancer.

Review Simulta
radiotherapy: init

Cited by 1 Publ

2'-Deoxyriboguan

Low doses of DNA-demethylating agents



Cell PRESS

Cancer Cell
Article

Transient Low Doses of DNA-Demethylating Agents Exert Durable Antitumor Effects on Hematological and Epithelial Tumor Cells

Hsing-Chen Tsai,[1,2,10] Hui Li,[2,10] Leander Van Neste,[3,10] Yi Cai,[2] Carine Robert,[4] Feyruz V. Rassool,[4] James J. Shin,[2,5] Kirsten M. Harbom,[2] Robert Beaty,[2] Emmanouil Pappou,[2,5] James Harris,[2,5] Ray-Whay Chiu Yen,[2] Nita Ahuja,[2,5] Malcolm V. Brock,[2,5] Vered Stearns,[2,6] David Feller-Kopman,[7] Lonny B. Yarmus,[7] Yi-Chun Lin,[8] Alana L. Welm,[8] Jean-Pierre Issa,[9] Il Minn,[2] William Matsui,[1,2] Yoon-Young Jang,[2] Saul J. Sharkis,[1,2] Stephen B. Baylin,[1,2,*] and Cynthia A. Zahnow[2,5,*]

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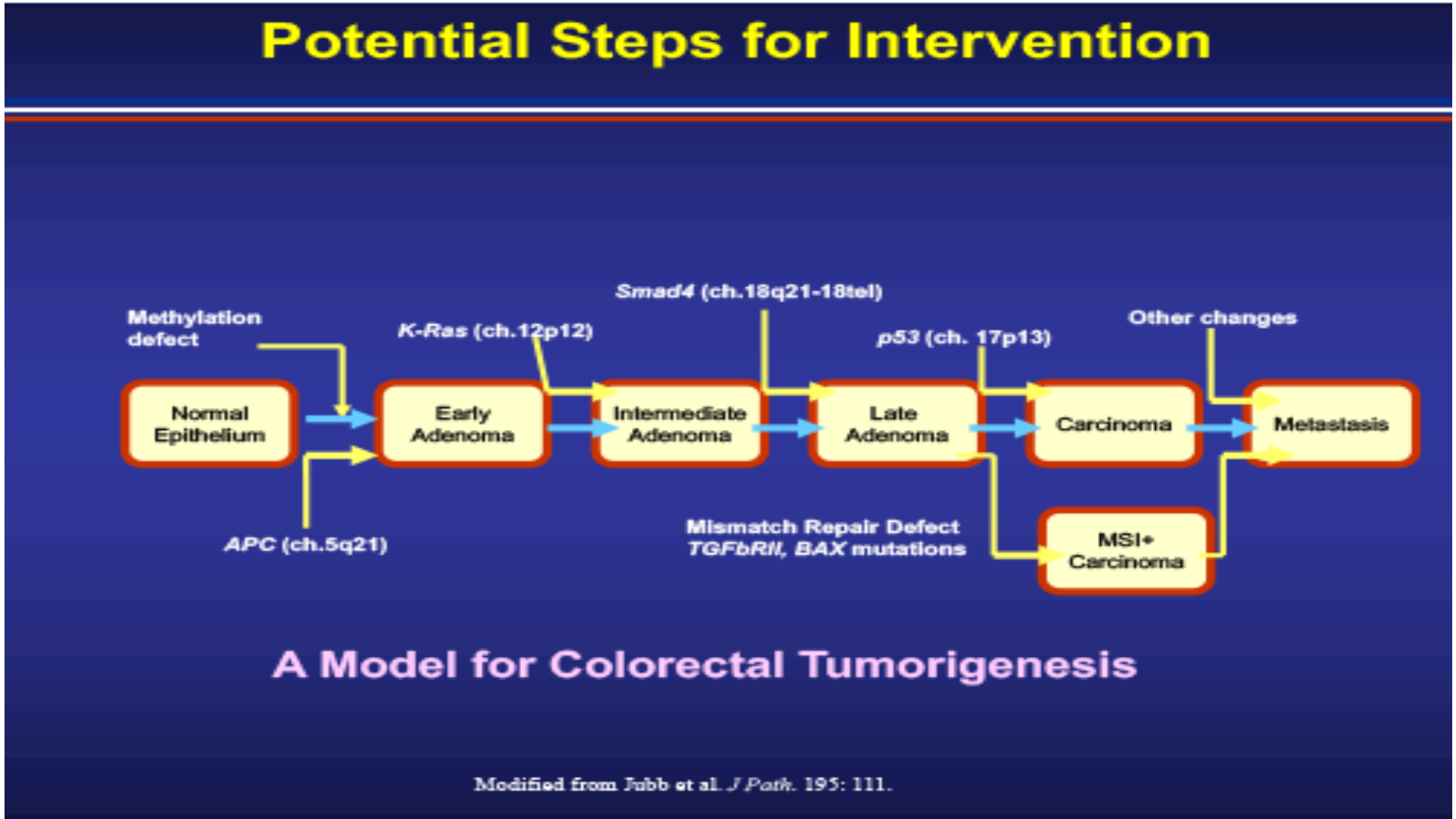
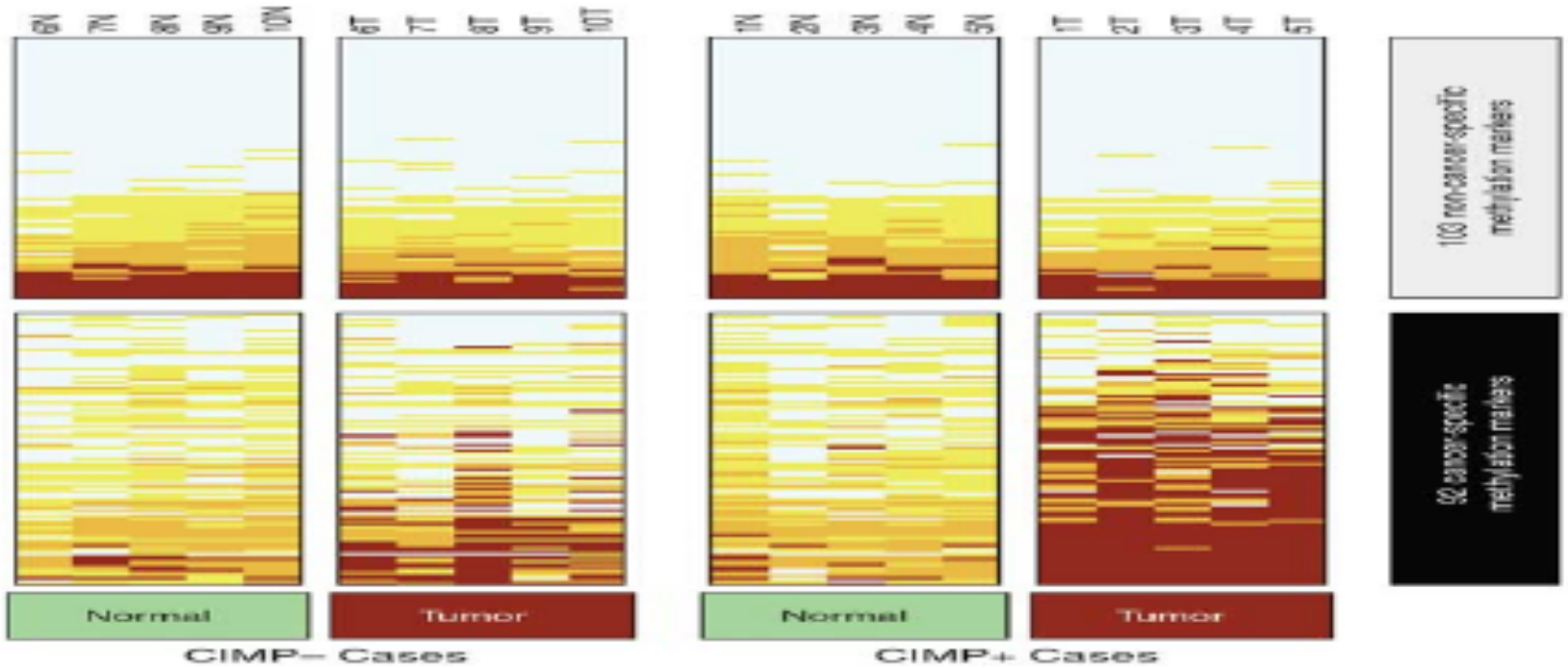
[4]Department of Radiation Oncology, Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[5]Department of Surgery, School of Medicine, Johns Hopkins University, Baltimore, MD 21231, USA
[6]Breast Cancer Program, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD 21231, USA
[7]Bronchoscopy and Interventional Pulmonology, Johns Hopkins Hospital, Baltimore, MD 21205, USA
[8]Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112, USA
[9]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030 USA
[10]These authors contributed equally to this work
*Correspondence: sbaylin@jhmi.edu (S.B.B.), zahnoci@jhmi.edu (C.A.Z.)
DOI 10.1016/j.ccr.2011.12.029

Intervention



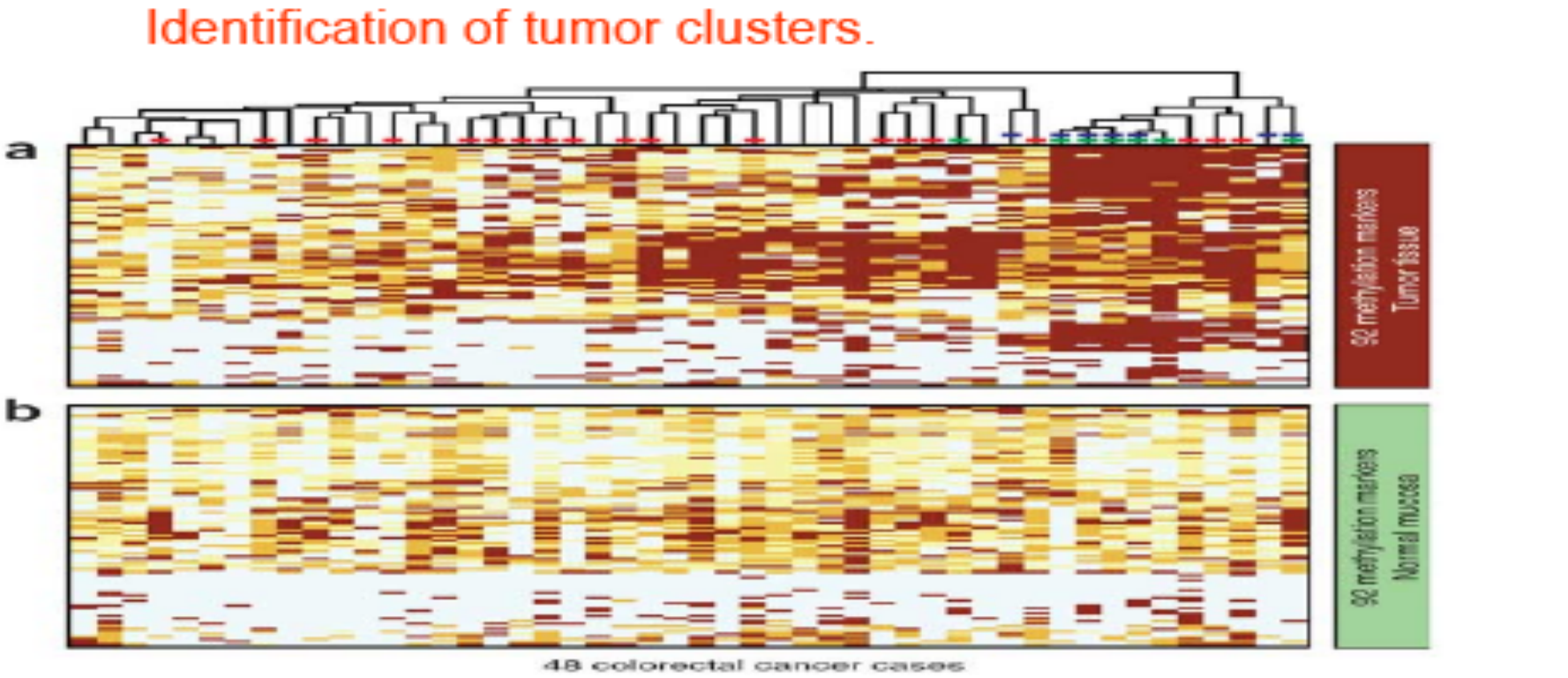
Microsatellite instability

CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer



Nature Genetics 38, 787 - 793

Tumor clusters

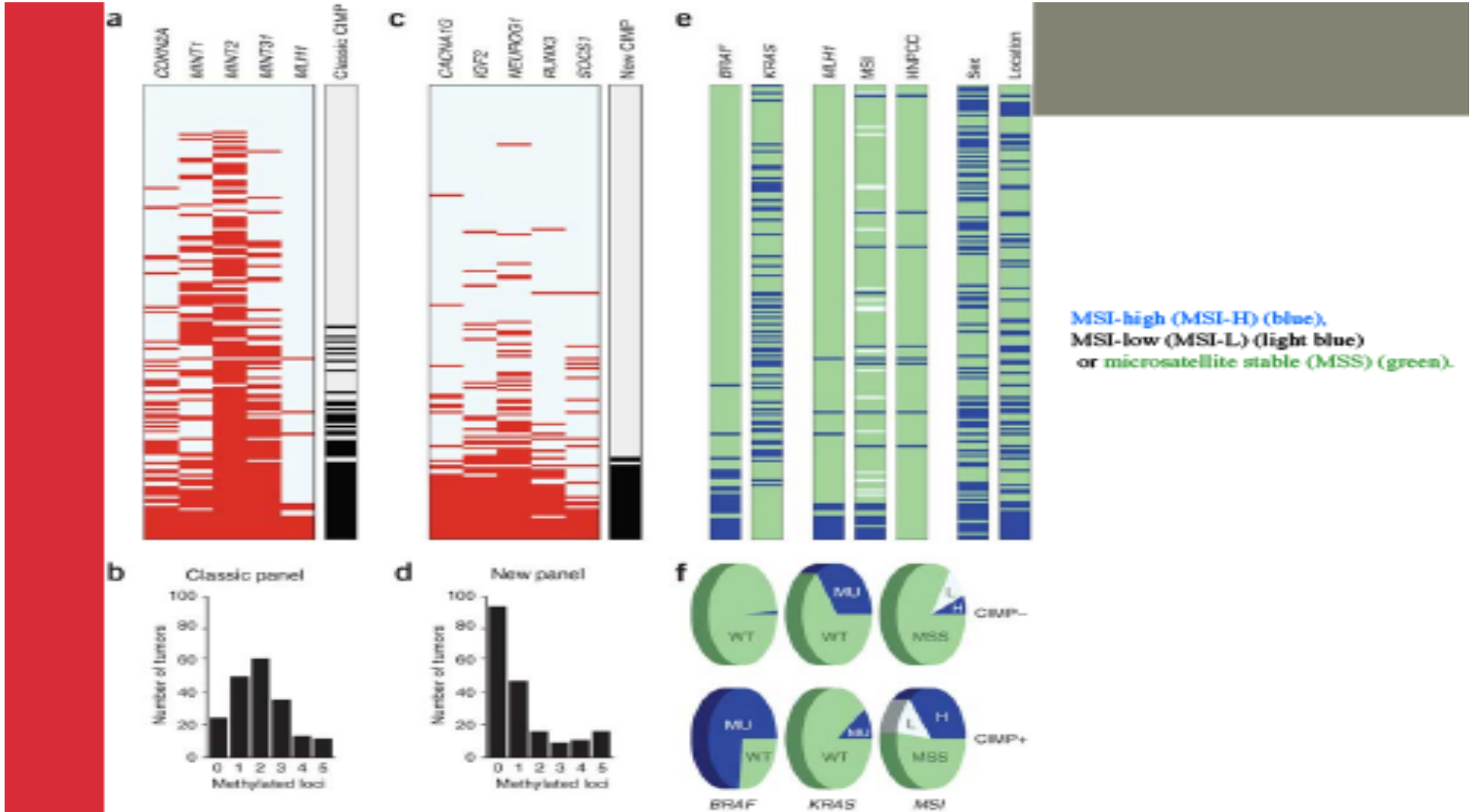


KRAS mutation indicated by a red rectangle overlaying the branch,
BRAF mutations indicated by a green rectangle
MSI-H cases designated with a blue rectangle.

48 Colorectal tumors

Nature Genetics **38**, 787 - 793

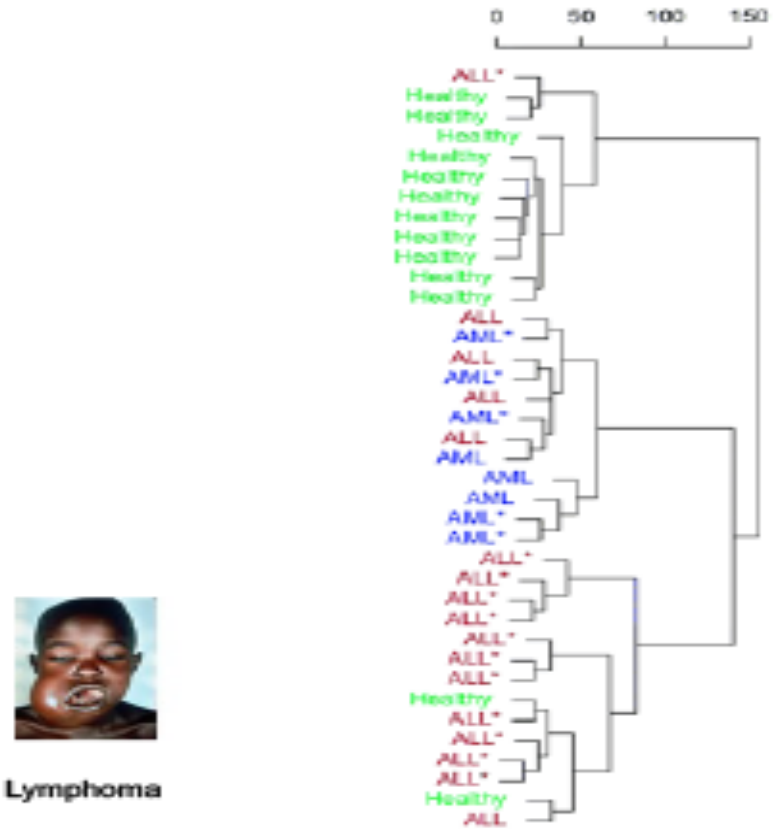
Genetic analysis



Methylation analysis

National Cancer Institute

Prediction of Tumor Class based on Methylation Analysis (AML and ALL)

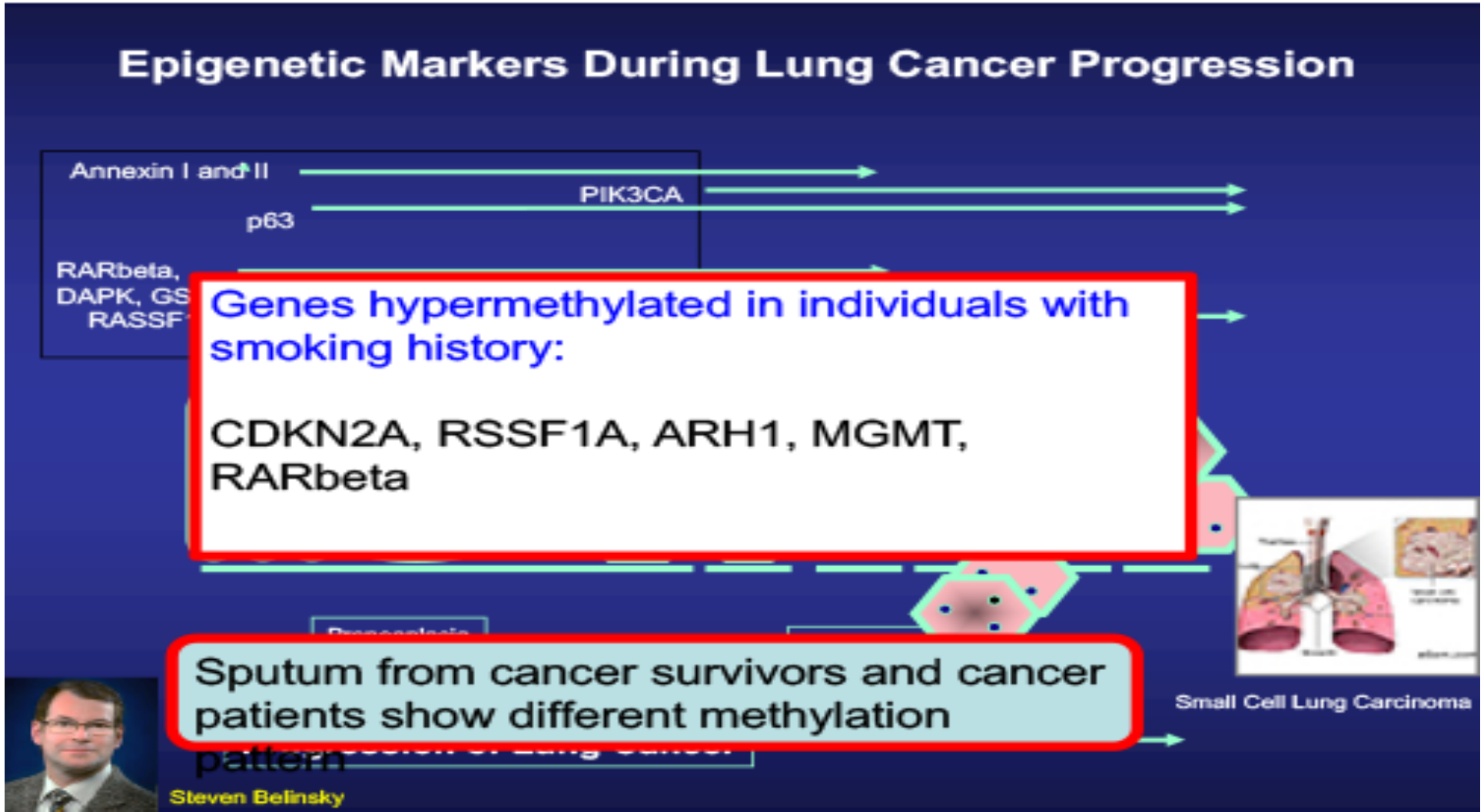


AML:Acute Myeloid Leukemia
ALL: Acute Lymphoblastic Leukemia

Lymphoma

Adorjan et al *Nuc Ac Res.* 30: e21

Epigenetic markers

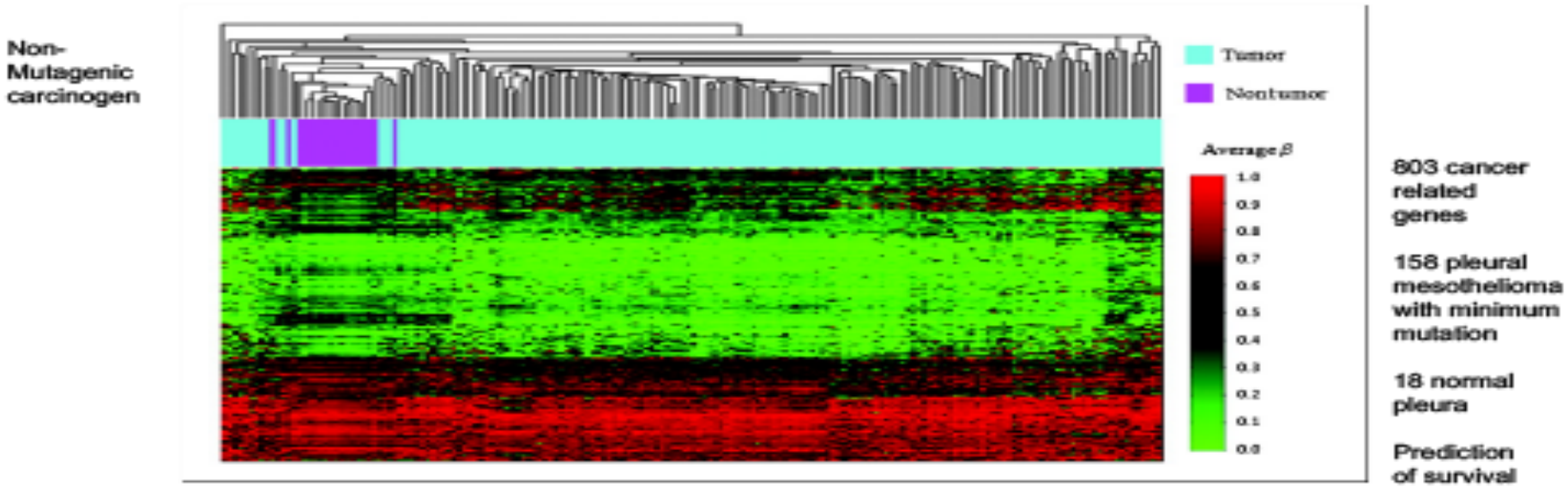


Mesothelioma

Unsupervised clustering of average {beta} values in tumor and nontumor pleura

ASBESTOS

MESOTHELIOMA

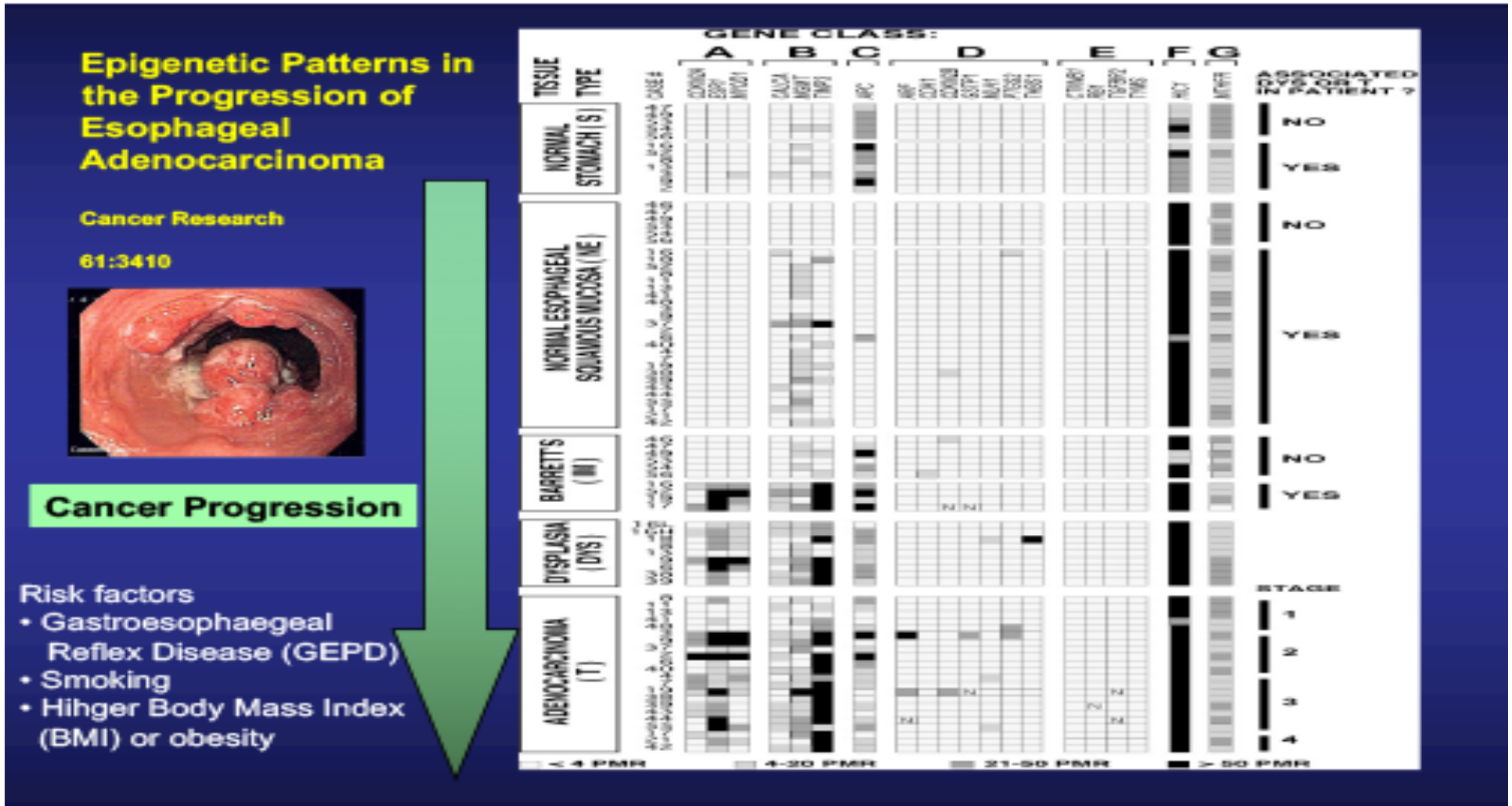


Christensen, B. C. et al. Cancer Res 2009;69:227-234

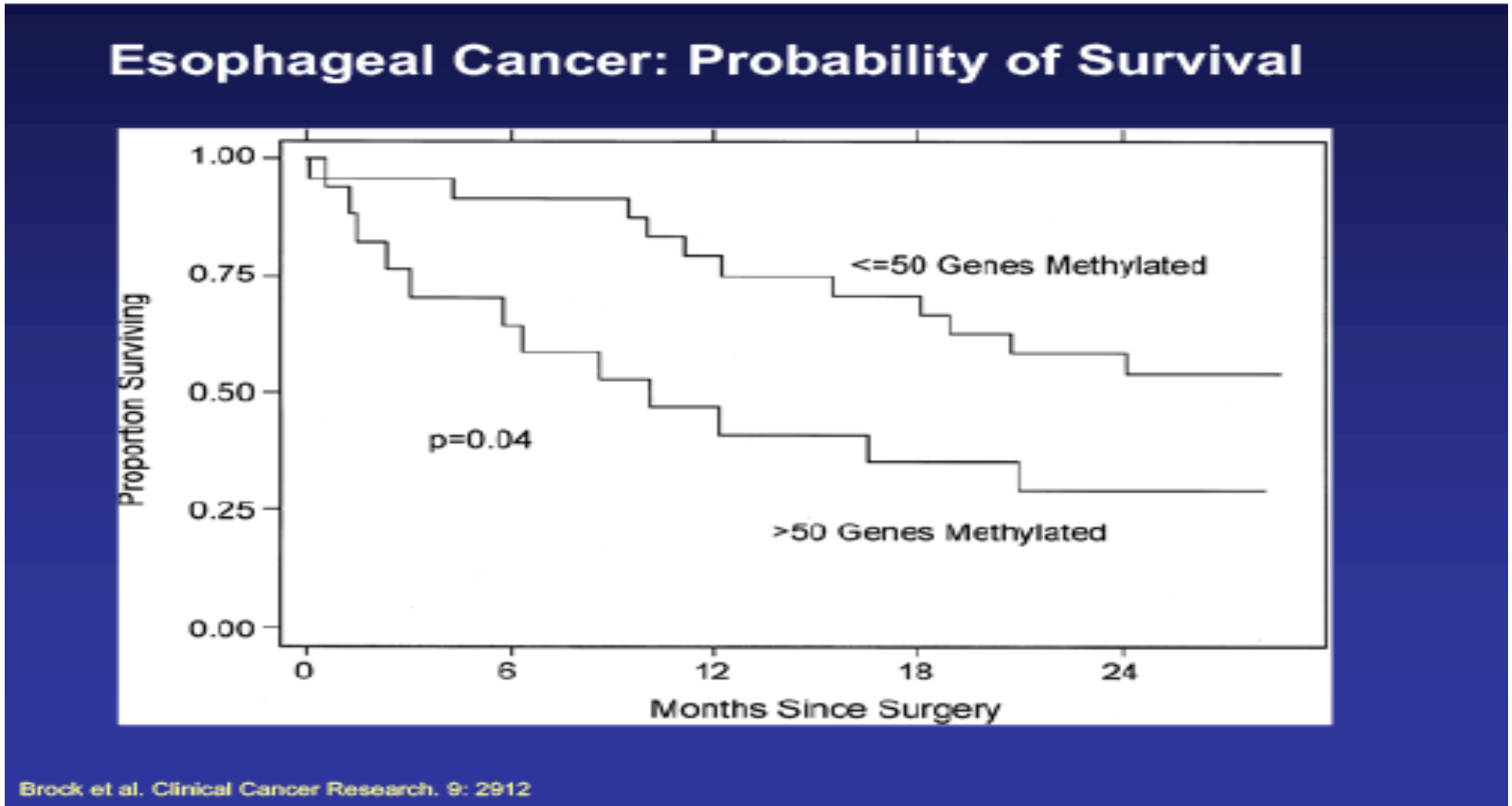
Epigenetic Profiles Distinguish Pleural Mesothelioma from Normal Pleura and Predict Lung Asbestos Burden and Clinical Outcome

Cancer Research

Epigenetic pattern



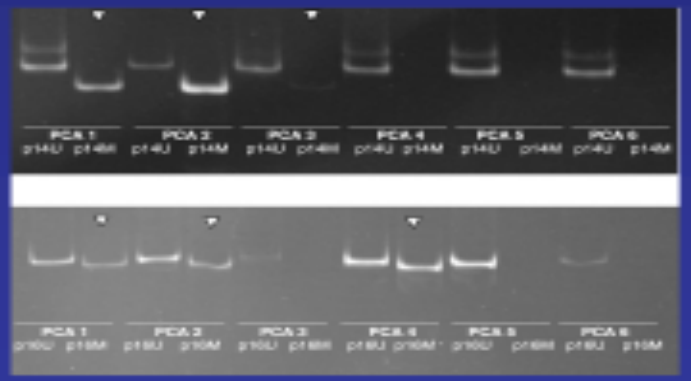
Esophageal cancer

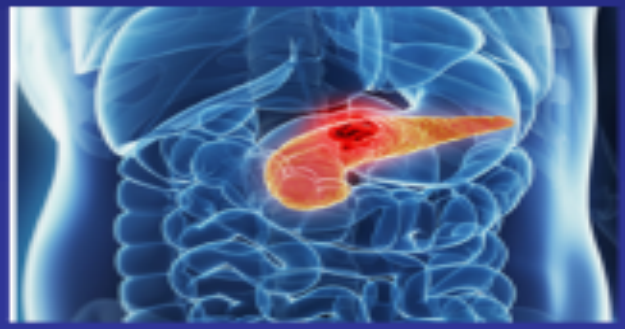


Pancreatic cancer

Pancreatic Cancer: Methylation of p14ARF and p16INK4a

Pancreatic Carcinoma (PCA) : 39	19/39	p16INK4a
Chronic Pancreatitis (CP) : 16	0/16	p16INK4a
Normal Pancreatogram (NAD) : 6	0/6	p16INK4a



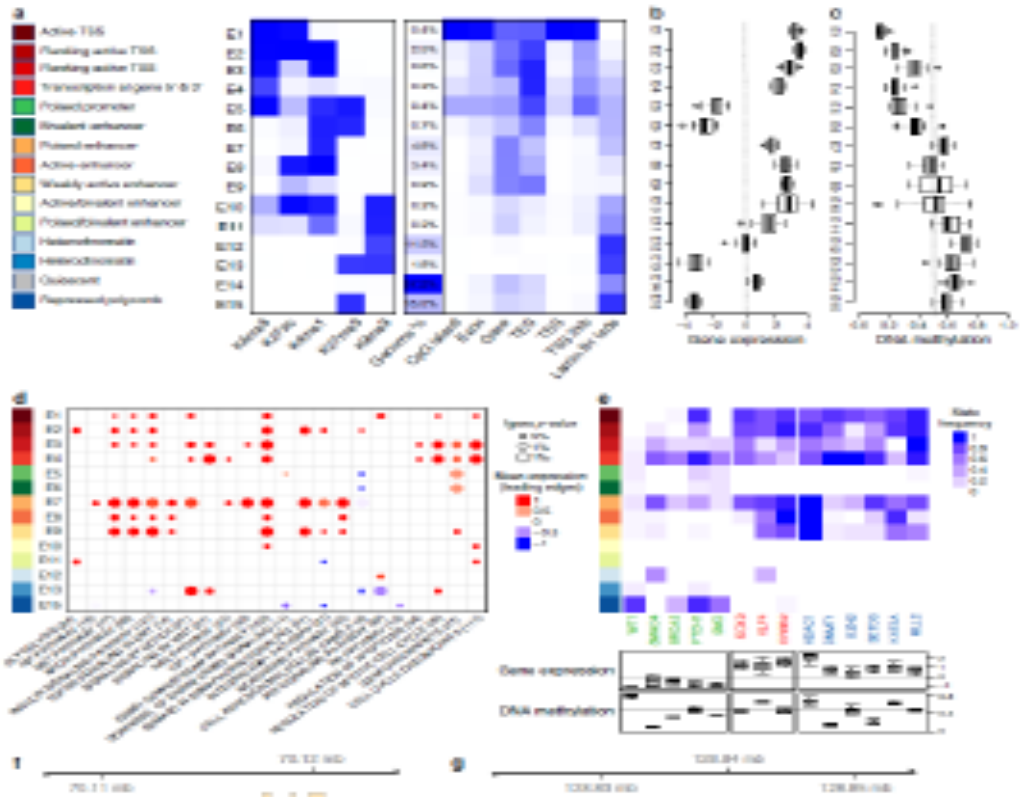


Sample: Pancreatic Fluid

(Klump et al. *Mol Cell Path* 88: 217)

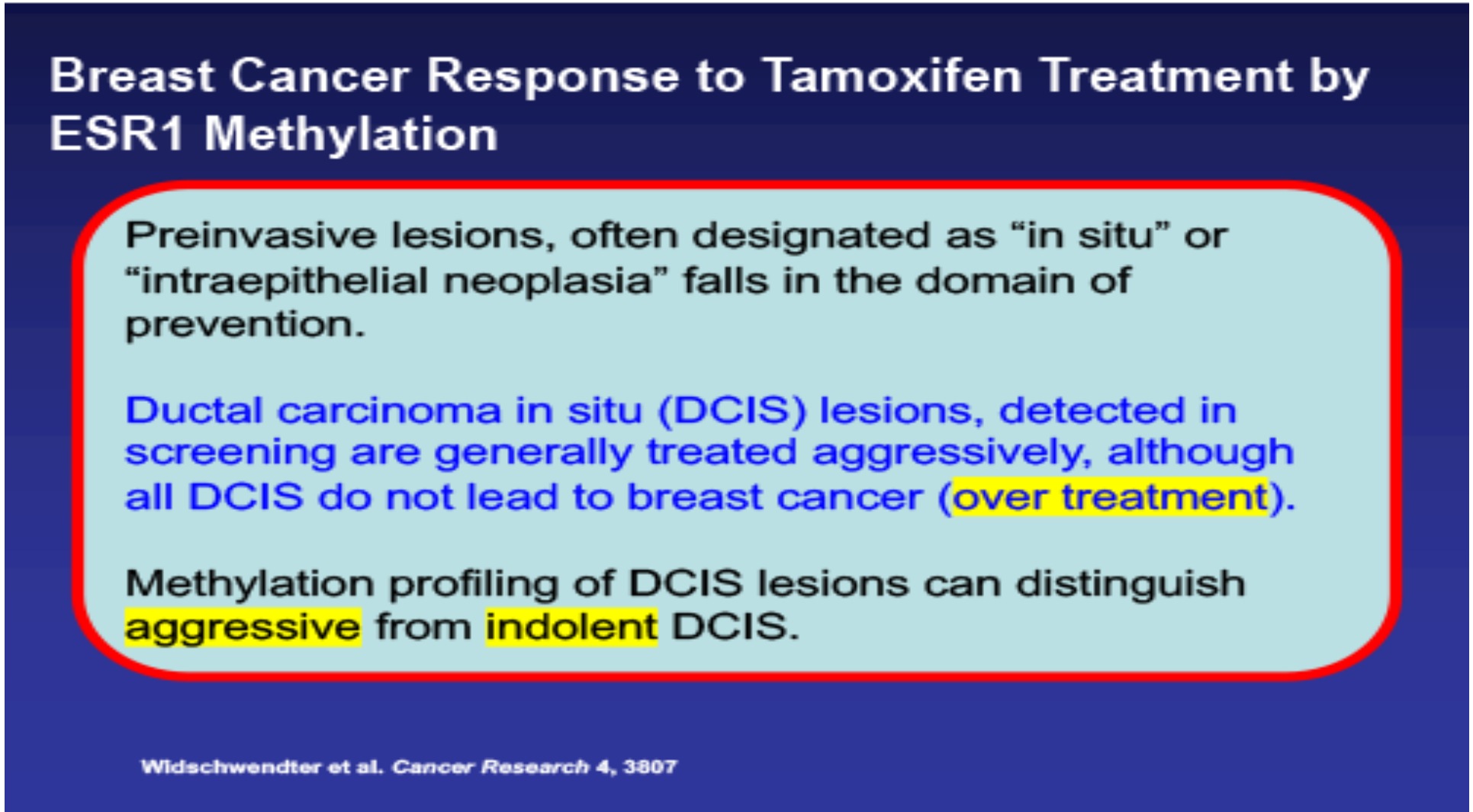
Chromatin states

Distinct chromatin states of human PDAC

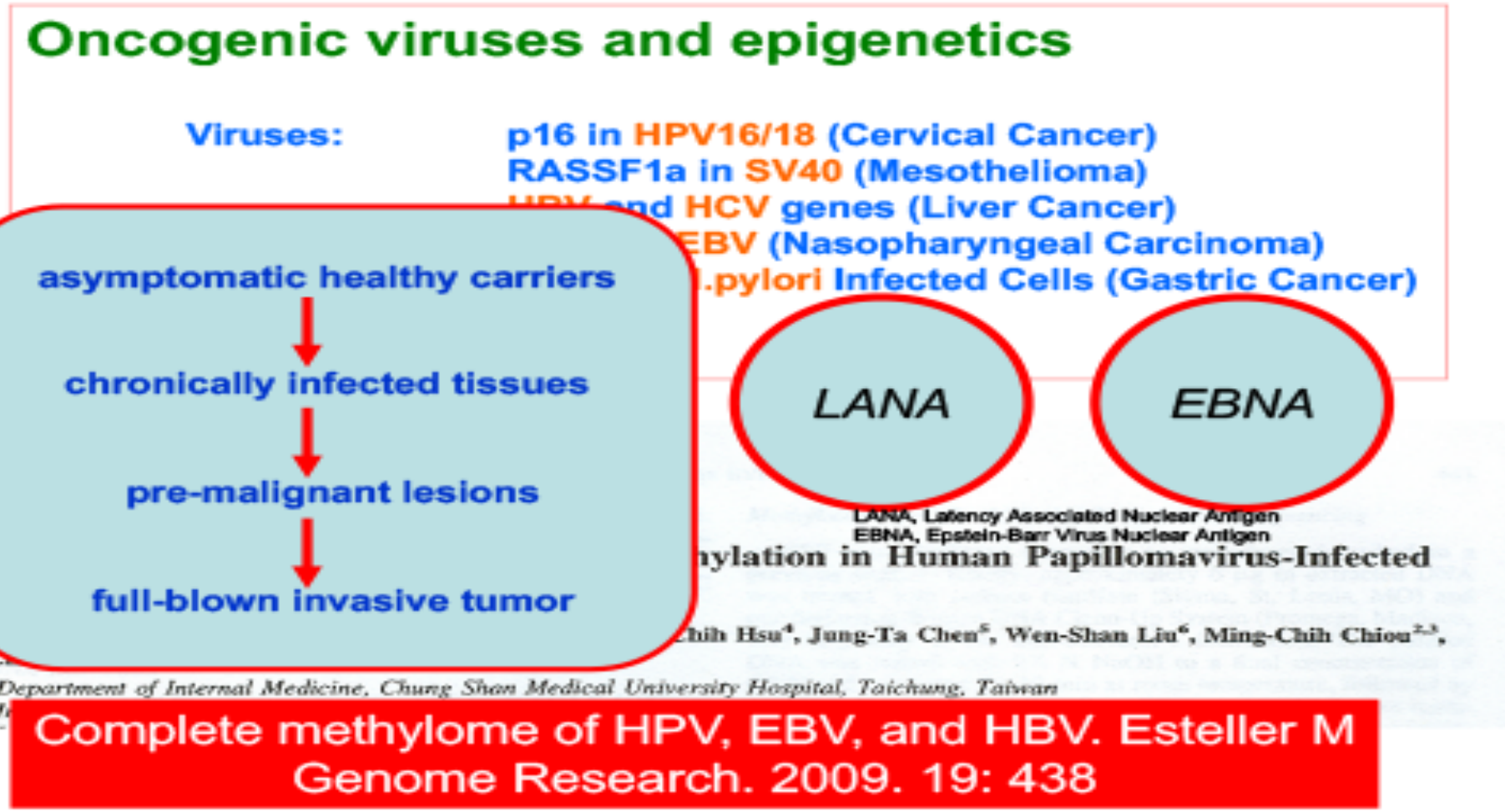


NATURE COMMUNICATIONS | (2018) 9:1978

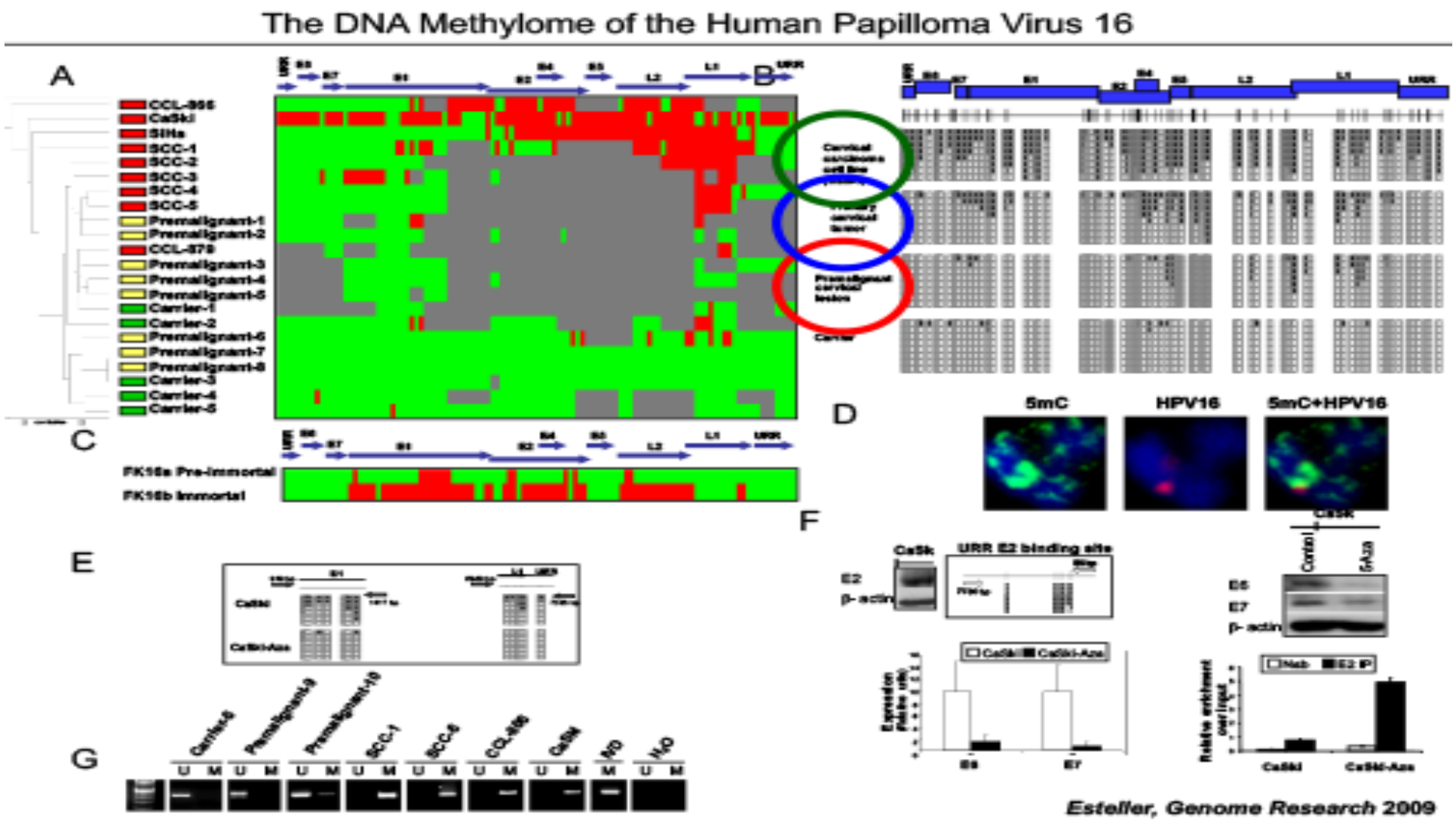
Breast cancer



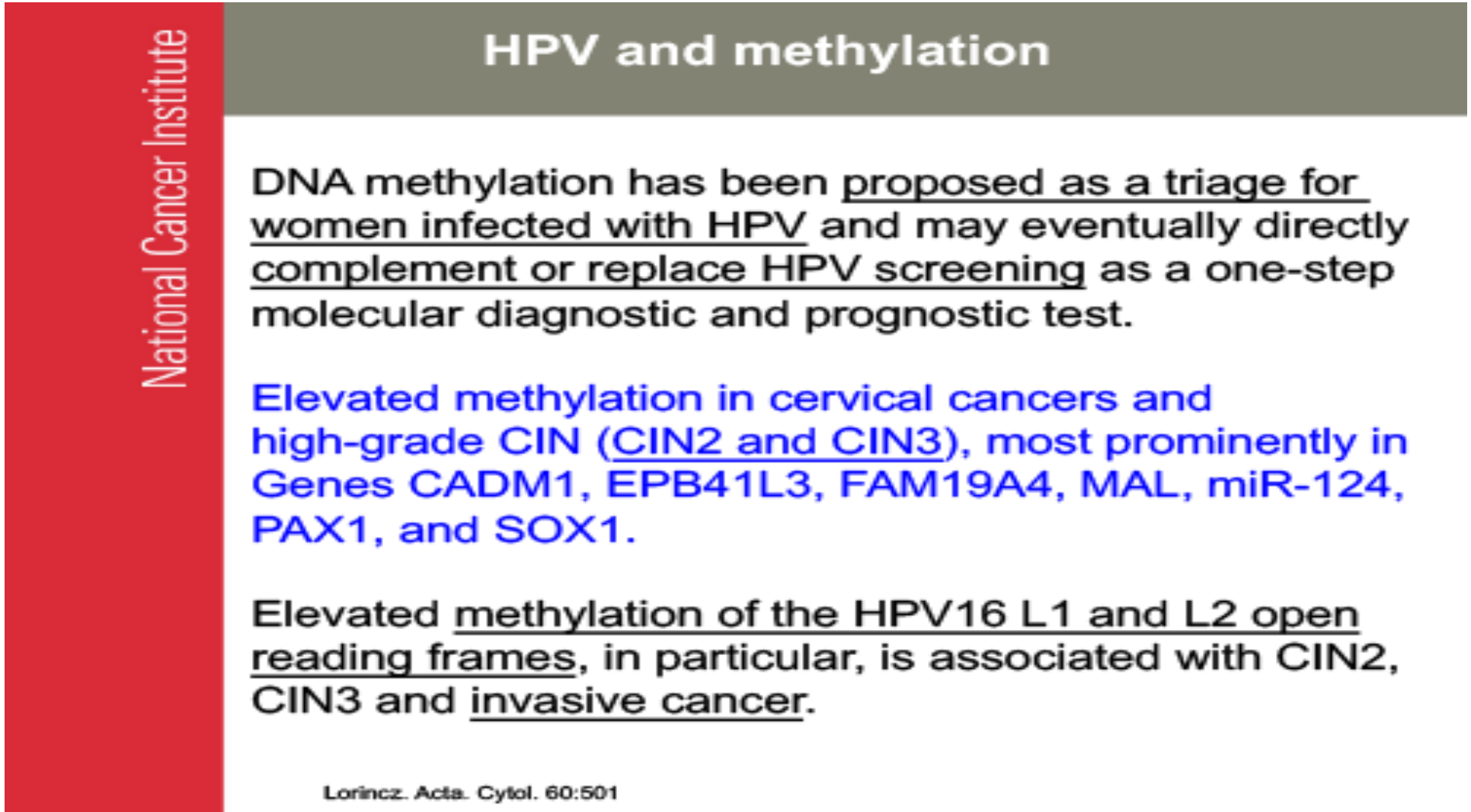
Organic viruses



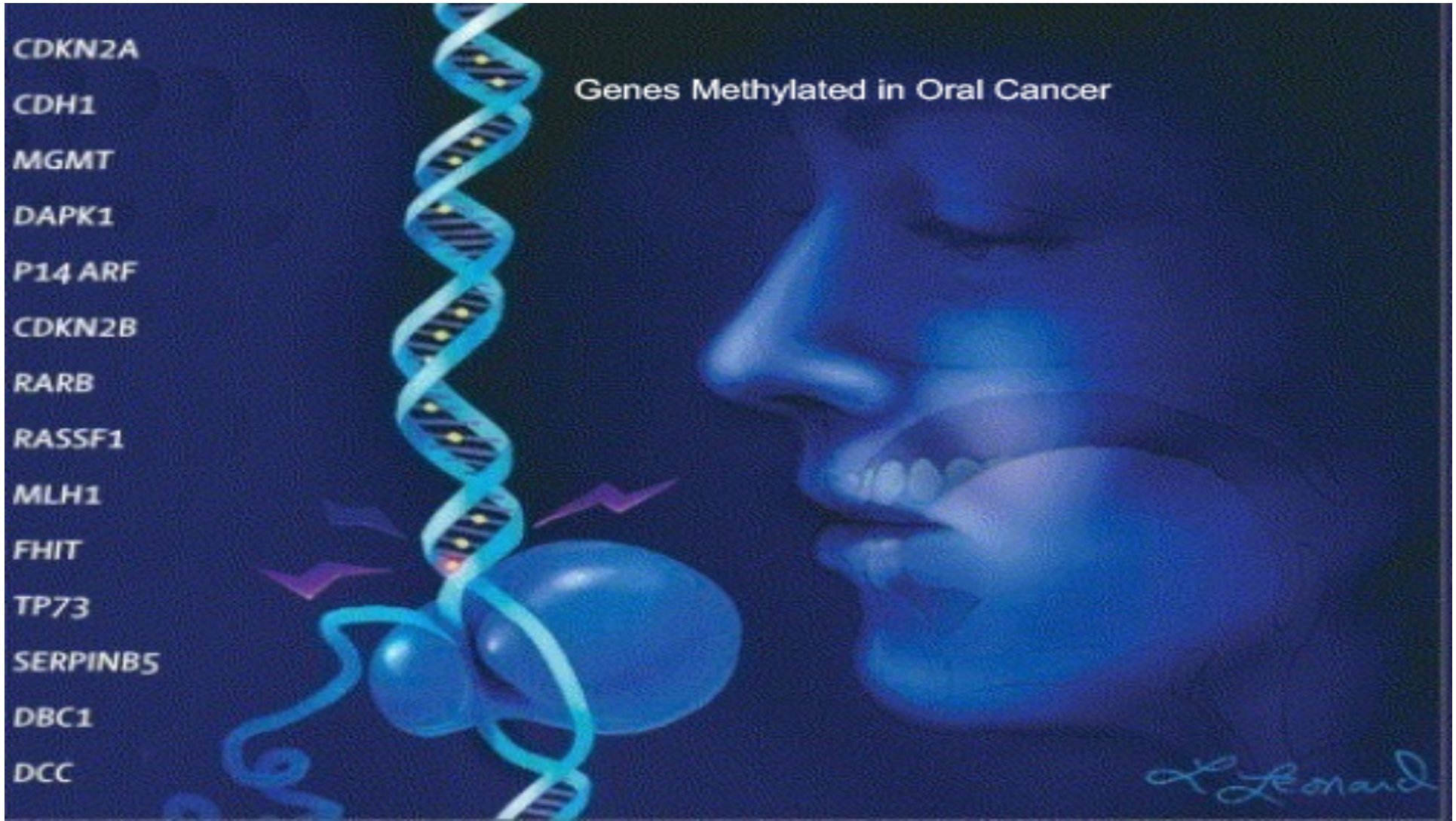
DNA methylation



HPV and methylation



Methylated genes



Immune system and epigenetics

Immune System and Epigenetics

Shin HJ et al.
Links STAT4 expression in human T cells is regulated by DNA methylation but not by promoter polymorphism.
J Immunol.175(11):7143-50.

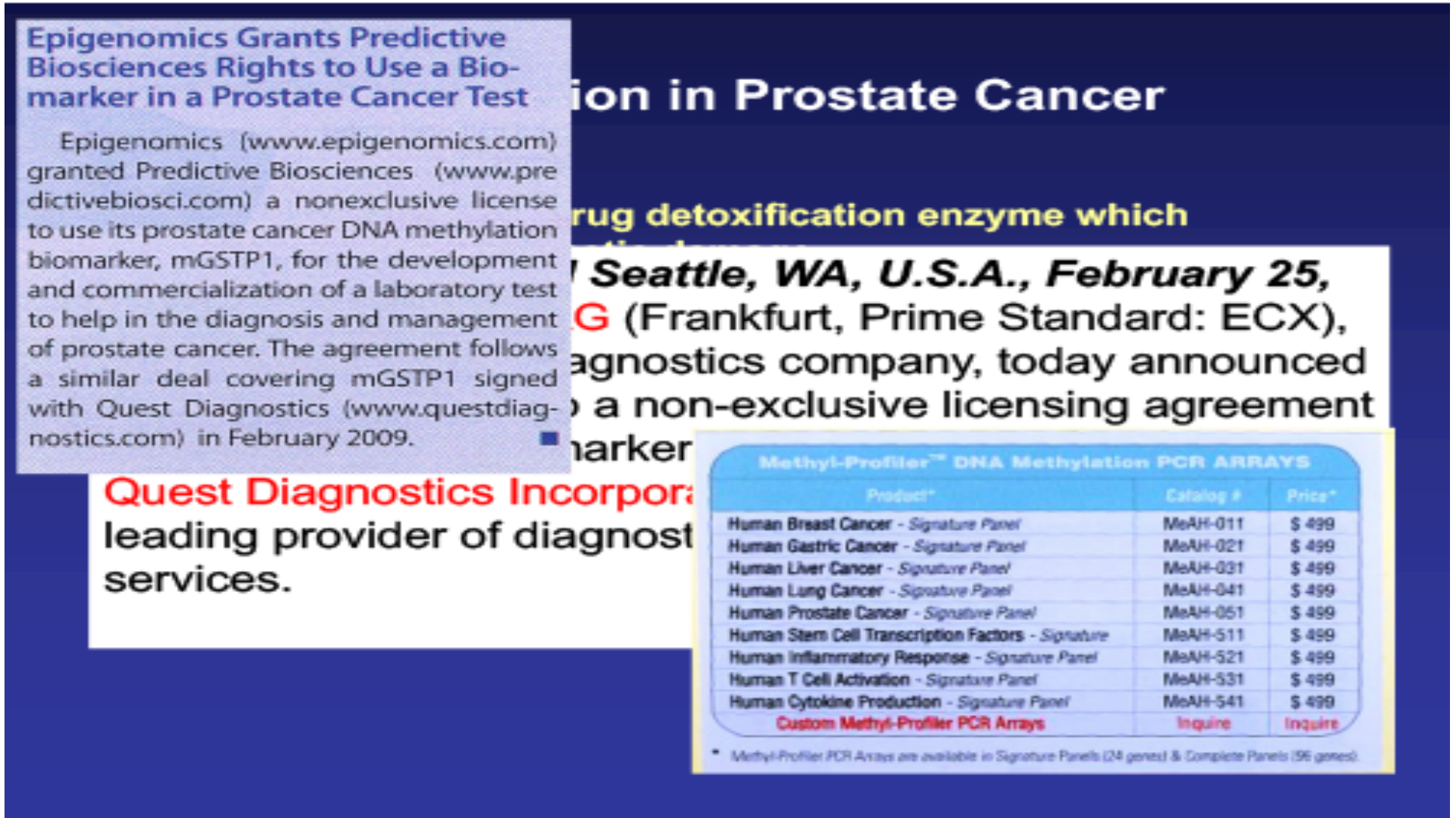
Espinoza CR, Feeney AJ.
The extent of histone acetylation correlates with the differential rearrangement frequency of individual VH genes in pro-B cells.
J Immunol. 175(10):6668-75.

Gasche JA, Hoffmann J, Boland CR, Goel A.
Interleukin-6 promotes tumorigenesis by altering DNA **methylation** in oral **cancer** cells.
Int J **Cancer**. 2011 Sep 1;129(5):1053-63.

Fujisawa T, Joshi BH, Puri RK.
Histone modification enhances the effectiveness of IL-13 receptor targeted immunotoxin in murine models of human pancreatic **cancer**.
J Transl Med. 2011 Apr 8;9:37.

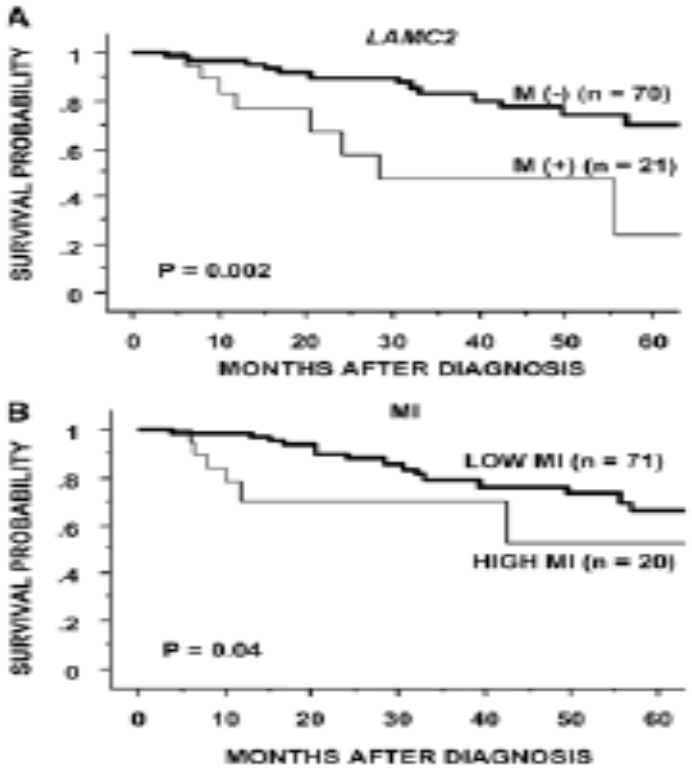
Tahara T et al.
Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-**methylation** in gastric **cancer**.
Int J Mol Med. 2010 Mar;25(3):471-7.

Biomarkers


Epigenomics Grants Predictive Biosciences Rights to Use a Bio-marker in a Prostate Cancer Test
Epigenomics (www.epigenomics.com) granted Predictive Biosciences (www.predictivebiosci.com) a nonexclusive license to use its prostate cancer DNA methylation biomarker, mGSTP1, for the development and commercialization of a laboratory test to help in the diagnosis and management of prostate cancer. The agreement follows a similar deal covering mGSTP1 signed with Quest Diagnostics (www.questdiagnostics.com) in February 2009.
ion in Prostate Cancer
rug detoxification enzyme which
Seattle, WA, U.S.A., February 25,
G (Frankfurt, Prime Standard: ECX),
agnostics company, today announced
a non-exclusive licensing agreement
arker
Quest Diagnostics Incorpora
leading provider of diagnost
services.
Methyl-Profiler™ DNA Methylation PCR ARRAYS
Product* Catalog # Price*
Human Breast Cancer - Signature Panel MeAH-011 $ 499
Human Gastric Cancer - Signature Panel MeAH-021 $ 499
Human Liver Cancer - Signature Panel MeAH-031 $ 499
Human Lung Cancer - Signature Panel MeAH-041 $ 499
Human Prostate Cancer - Signature Panel MeAH-051 $ 499
Human Stem Cell Transcription Factors - Signature MeAH-511 $ 499
Human Inflammatory Response - Signature Panel MeAH-521 $ 499
Human T Cell Activation - Signature Panel MeAH-531 $ 499
Human Cytokine Production - Signature Panel MeAH-541 $ 499
Custom Methyl-Profiler PCR Arrays Inquire Inquire
* Methyl-Profiler PCR Arrays are available in Signature Panels (24 genes) & Complete Panels (96 genes).

Bladder cancer methylation

Bladder Cancer
Methylation of LAMC2 in Exfoliated Cells Isolated from Urine

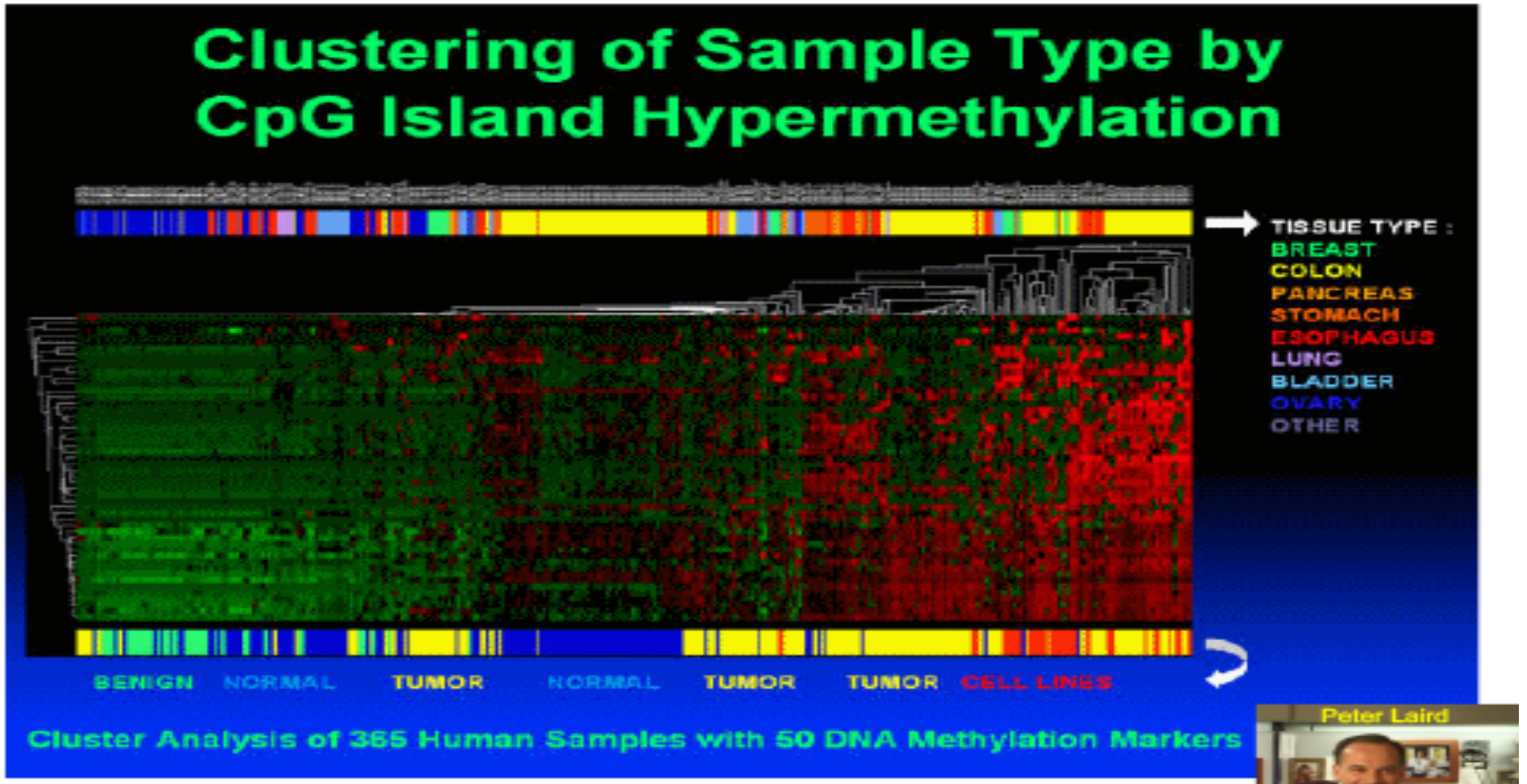


Another Study:
Schistosomes and Bladder Cancer

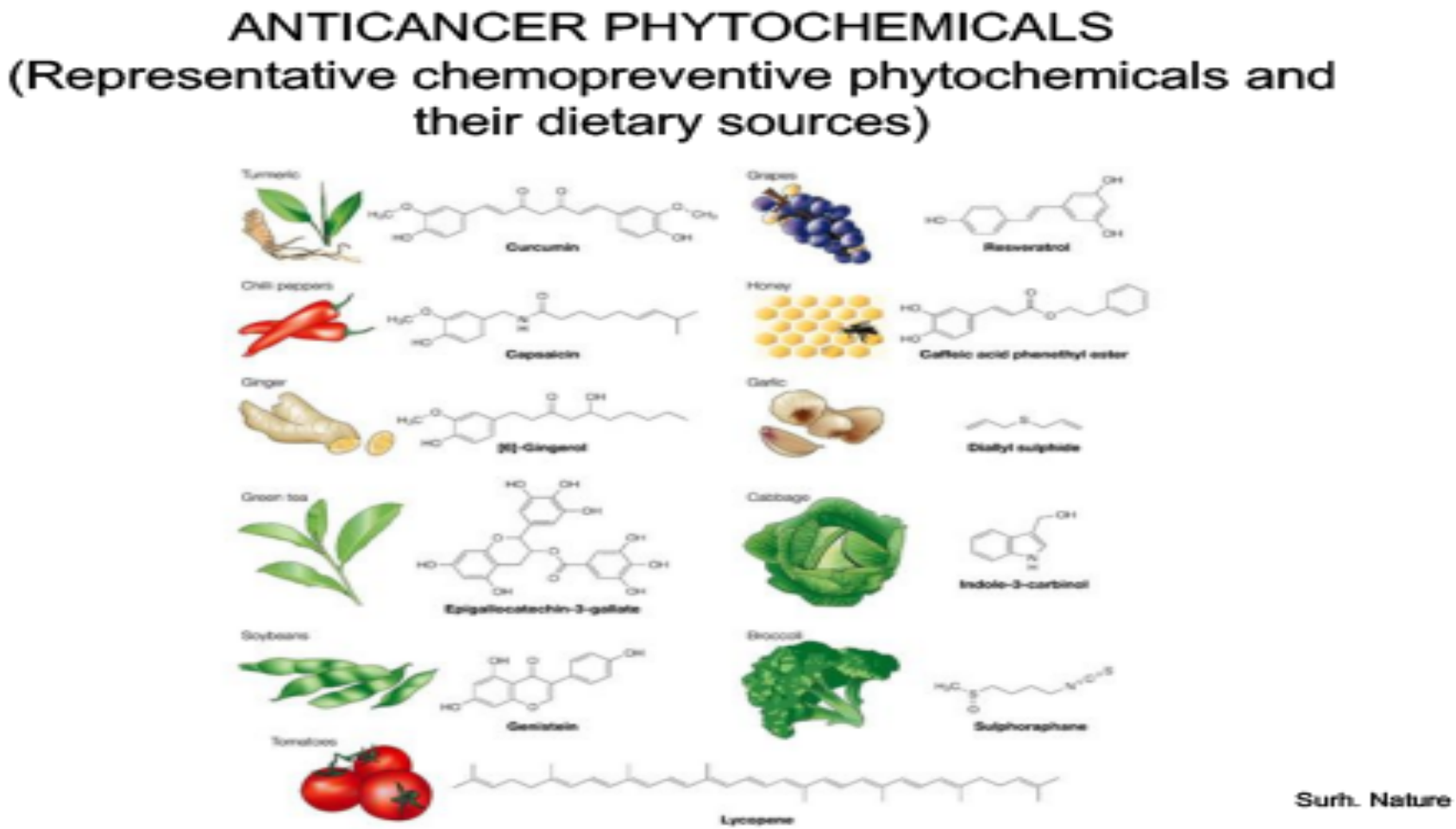
MI, Methylation Index

(Sathyanarayana et al. *Can Res* 64: 1425)

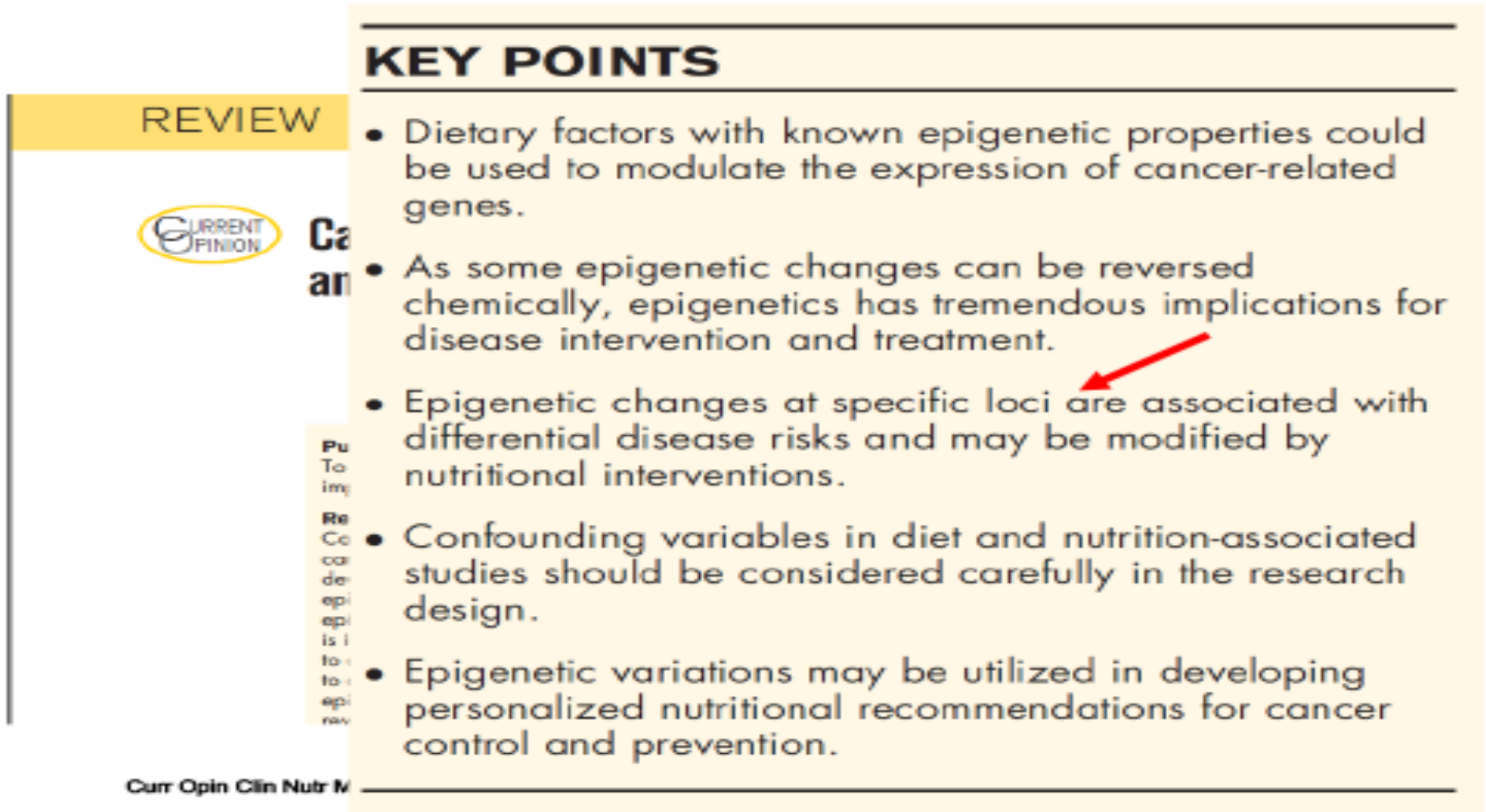
CpG island hypermethylation



Anticancer phytochemicals



Key points



REVIEW

CURRENT OPINION

KEY POINTS

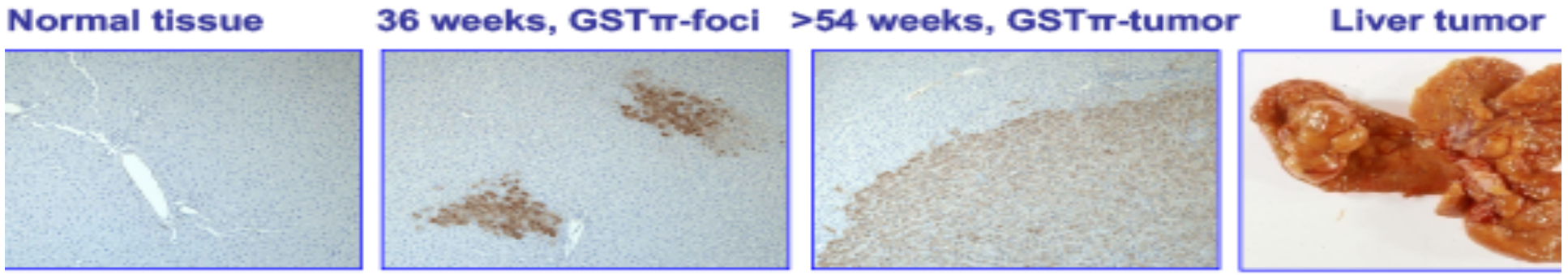
- Dietary factors with known epigenetic properties could be used to modulate the expression of cancer-related genes.
- As some epigenetic changes can be reversed chemically, epigenetics has tremendous implications for disease intervention and treatment.
- Epigenetic changes at specific loci are associated with differential disease risks and may be modified by nutritional interventions.
- Confounding variables in diet and nutrition-associated studies should be considered carefully in the research design.
- Epigenetic variations may be utilized in developing personalized nutritional recommendations for cancer control and prevention.

Curr Opin Clin Nutr M

Carcinogenesis

METHYL-DEFICIENT MODEL OF ENDOGENOUS HEPATOCARCINOGENESIS

- Chronic deficiency in the methyl donors methionine, choline, folic acid and vitamin B_{12}
- No exogenous carcinogen added
- No genetic manipulation
- Hepatocellular carcinoma in 14-16 months in male rats and certain mouse strains
- Sequence of pathological changes similar to the development of hepatocellular carcinoma in humans



Igor et al. 2007 (personal communication)

Hepatocellular epigenetics

Nutr Cancer. 2016 Jul;68(5):719-33. doi: 10.1080/01635581.2016.1180410. Epub 2016 Jun 8.

Nutritional Epigenetics and the Prevention of Hepatocellular Carcinoma with Bioactive Food Constituents.

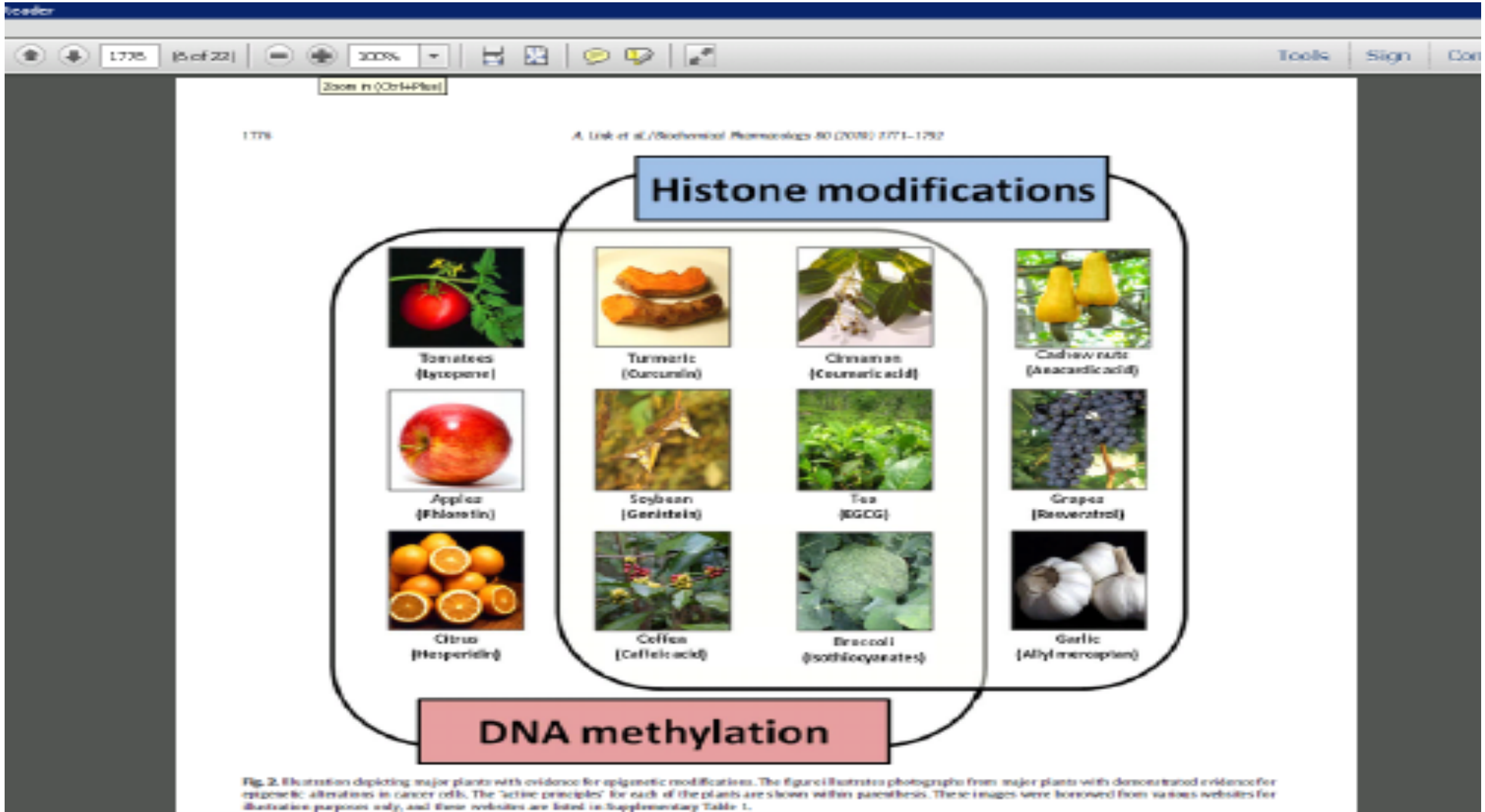
Moreno FS[1], Heidor R[1], Pogribny IP[2].

Author information

Abstract

Hepatocellular carcinoma (HCC) is an aggressive and life-threatening disease often diagnosed at intermediate or advanced stages, which substantially limits therapeutic approaches to its successful treatment. This indicates that the prevention of HCC may be the most promising strategy in reducing its incidence and mortality. Emerging evidence indicates that numerous nutrients and nonnutrient dietary bioactive components can reduce the occurrence and/or delay the development of HCC through modifications of deregulated epigenetic mechanisms. This review examines the existing knowledge on the epigenetic mechanism-based studies in in vitro and in vivo models of HCC on the chemopreventive potential of epigenetic food components, including dietary methyl-group donors, epigallocatechin-3-gallate, sodium butyrate, resveratrol, curcumin, and sulforaphane, on liver carcinogenesis. Future direction and potential challenges in the effective use of bioactive food constituents in the prevention of HCC are highlighted and discussed.

Epigenetic foods



Research opportunities

National Cancer Institute

Research Opportunities and Challenges

Will inclusion of epigenetic markers help in identification of new risk factors (modifiable factors and host factors) in different races and ethnic groups?

Will epigenetic markers in cohort and case-control studies improve sensitivity and specificity of markers and help in identifying high-risk populations?

Are genetic and epigenetic events correlated during cancer development?

Are there race/ethnicity specific miRNAs and noncoding RNAs?

How can we use this information for better define cancer subcategories?

How can we overcome EWAS technical challenges?

Christopher Plass (Heidelberg)

Nancy Kiviat (Seattle)

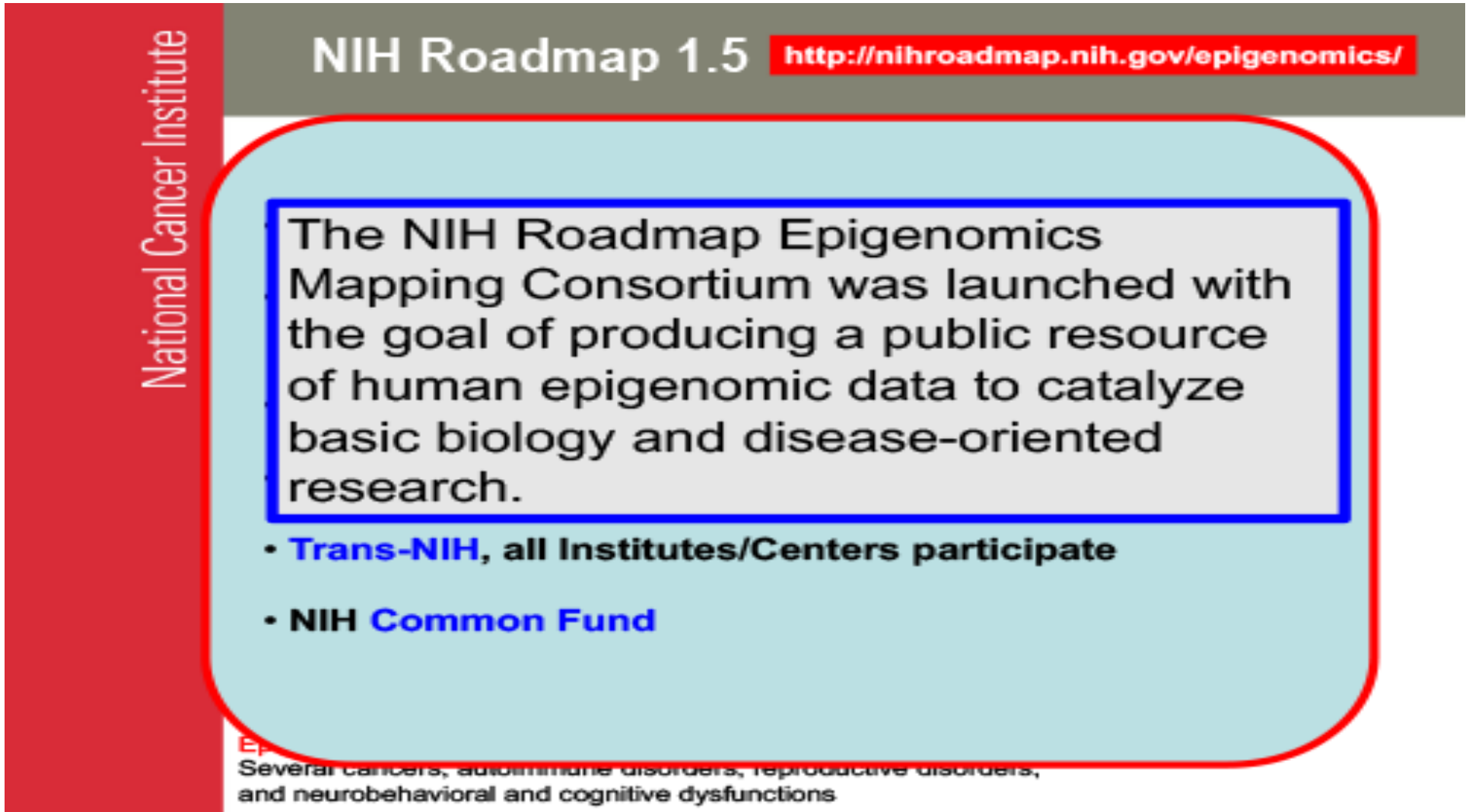
Christine Ambrosone (Roswell Park, Buffalow)

How to address challenges

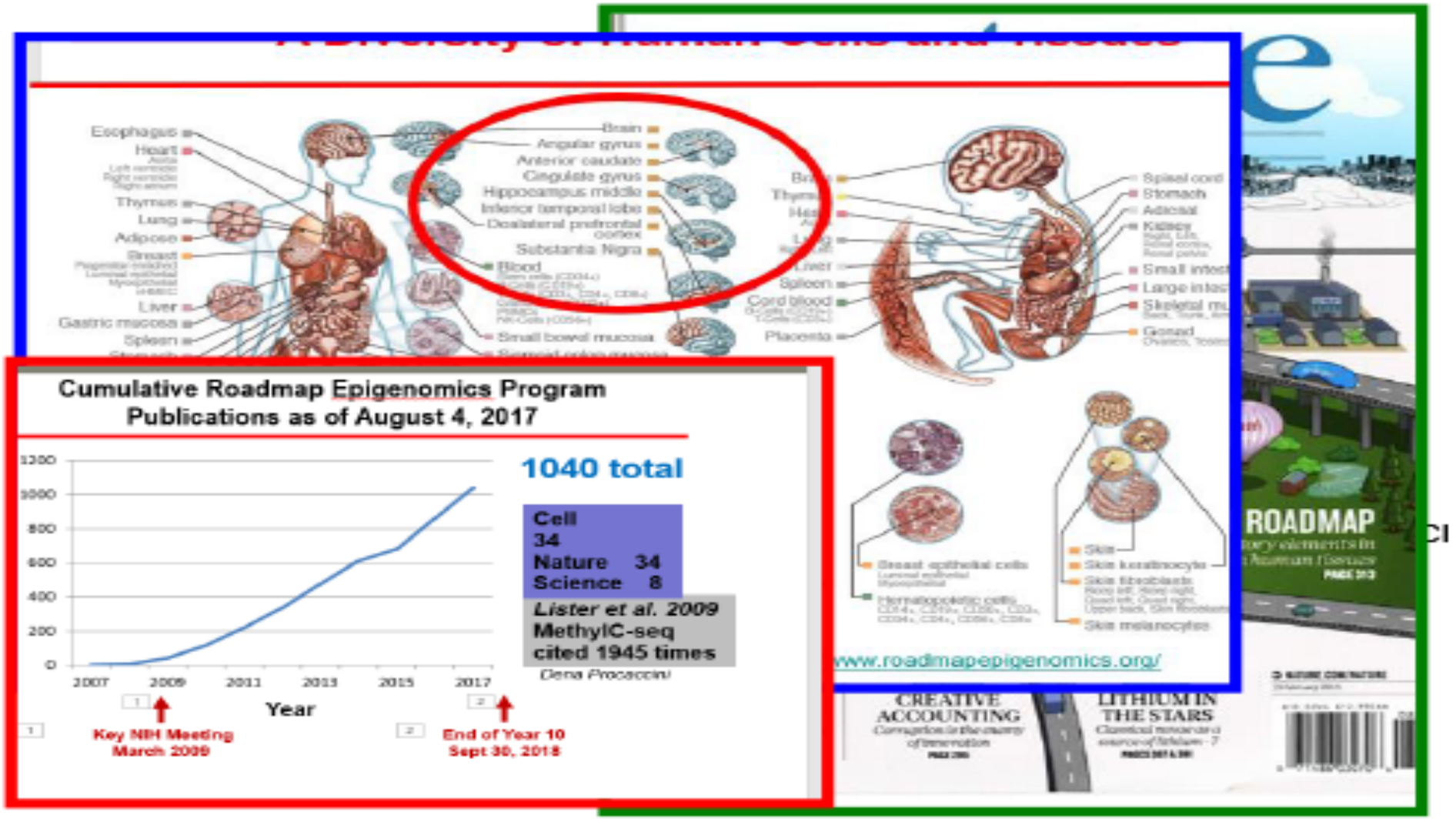
National Cancer Institute

How are we addressing these challenges?

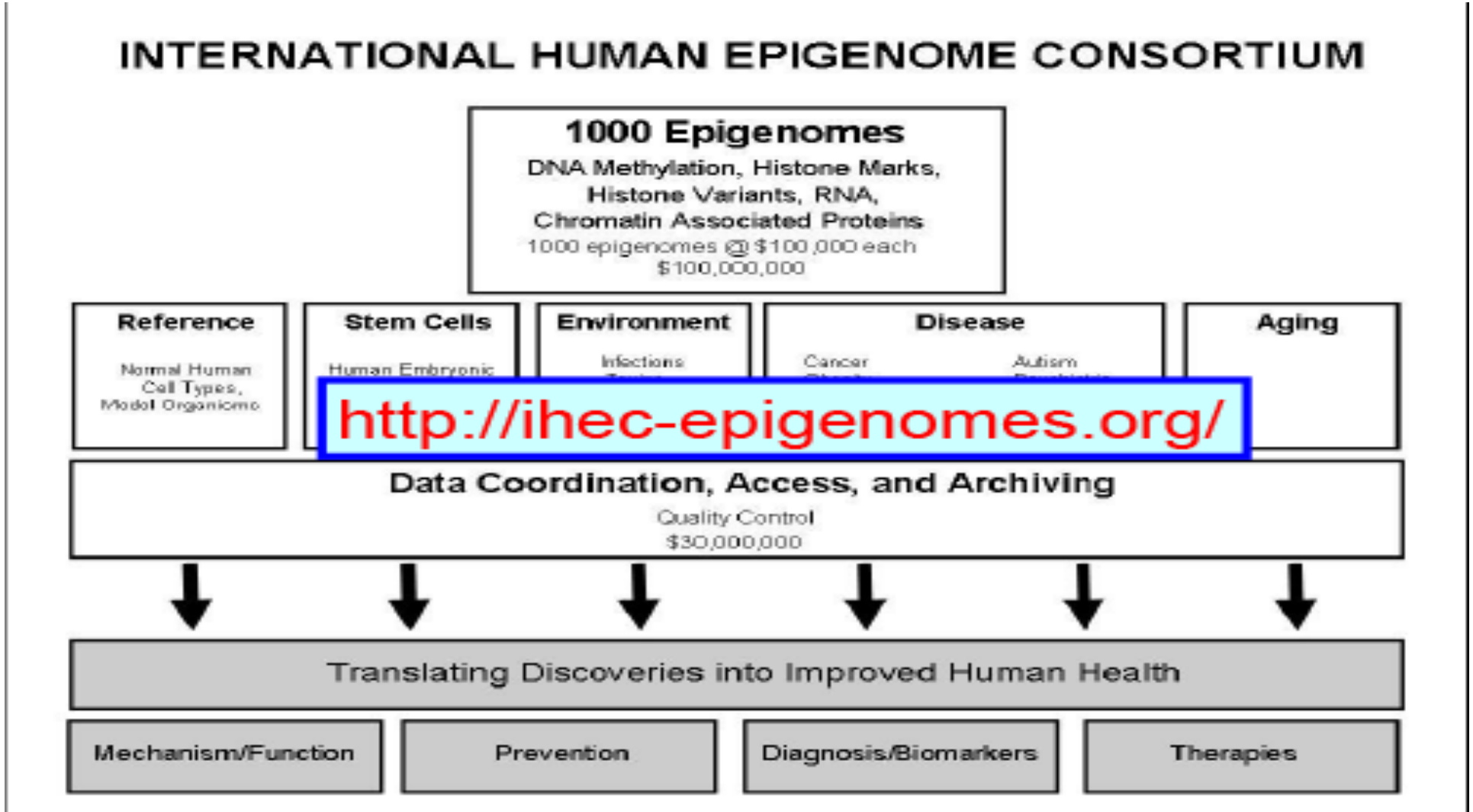
NIH Roadmap


National Cancer Institute
NIH Roadmap 1.5
http://nihroadmap.nih.gov/epigenomics/
The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research.
• Trans-NIH, all Institutes/Centers participate
• NIH Common Fund
and neurobehavioral and cognitive dysfunctions

Roadmap


Esophagus
Heart
Thymus
Lung
Adipose
Liver
Gastric mucosa
Spleen
Brain
Angular gyrus
Anterior caudate
Cingulate gyrus
Hippocampus middle
Inferior temporal lobe
Dorsolateral prefrontal cortex
Substantia Nigra
Blood
Small bowel mucosa
Cumulative Roadmap Epigenomics Program
Publications as of August 4, 2017
1200
1000
800
600
400
200
0
2007
2009
2011
2013
2015
2017
Year
1040 total
Cell 34
Nature 34
Science 8
Lister et al. 2009
MethylC-seq
cited 1945 times
Dena Procaccini
Key NIH Meeting
March 2009
End of Year 10
Sept 30, 2018
www.roadmapepigenomics.org/
ROADMAP
CREATIVE ACCOUNTING
LITHIUM IN THE STARS

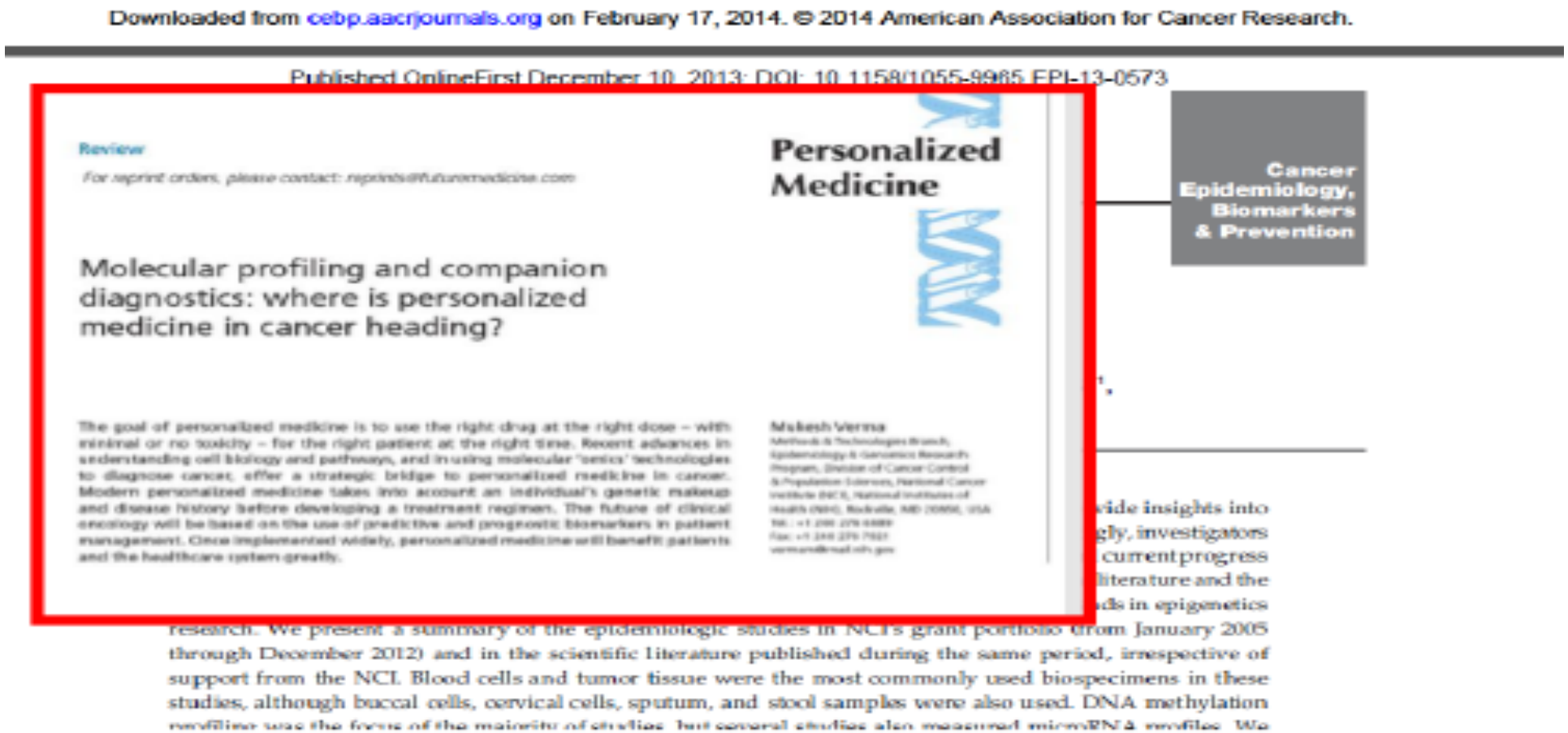
Epigenome consortium



IHEC


IHEC
About
Research
Outcomes
Epigenomics
News+Events
Links
The International Human Epigenome Consortium (IHEC) unites scientists from all over the world working together to achieve one common goal:
Welcome to IHEC
Lectures
Research

Molecular profiling



Published OnlineFirst December 10, 2013; DOI: 10.1158/1055-9965.EPI-13-0573

Review

Personalized Medicine

Molecular profiling and companion diagnostics: where is personalized medicine in cancer heading?

The goal of personalized medicine is to use the right drug at the right dose – with minimal or no toxicity – for the right patient at the right time. Recent advances in understanding cell biology and pathways, and in using molecular 'omics' technologies to diagnose cancer, offer a strategic bridge to personalized medicine in cancer. Modern personalized medicine takes into account an individual's genetic makeup and disease history before developing a treatment regimen. The future of clinical oncology will be based on the use of predictive and prognostic biomarkers in patient management. Once implemented widely, personalized medicine will benefit patients and the healthcare system greatly.

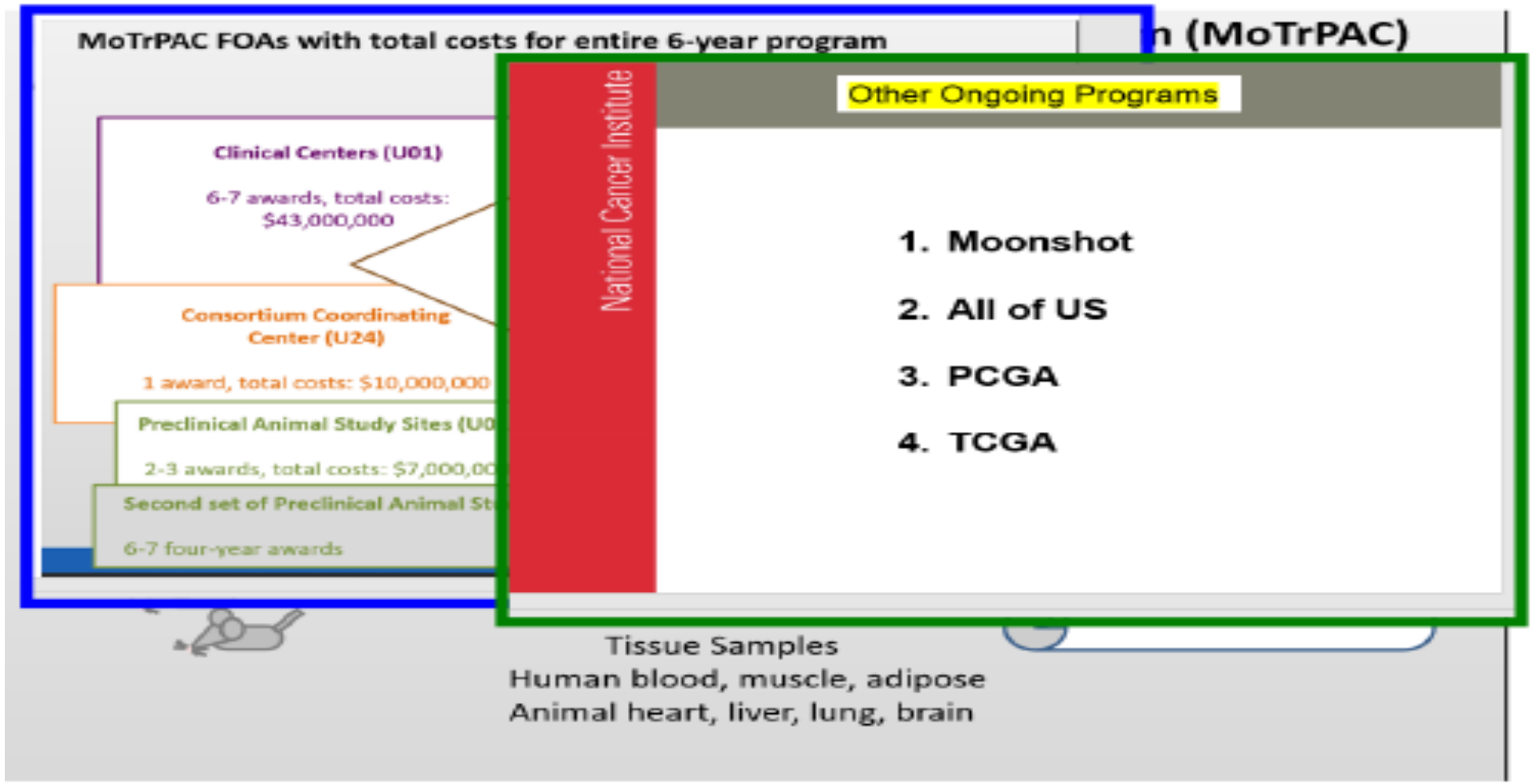
Mukesh Verma

Cancer Epidemiology, Biomarkers & Prevention

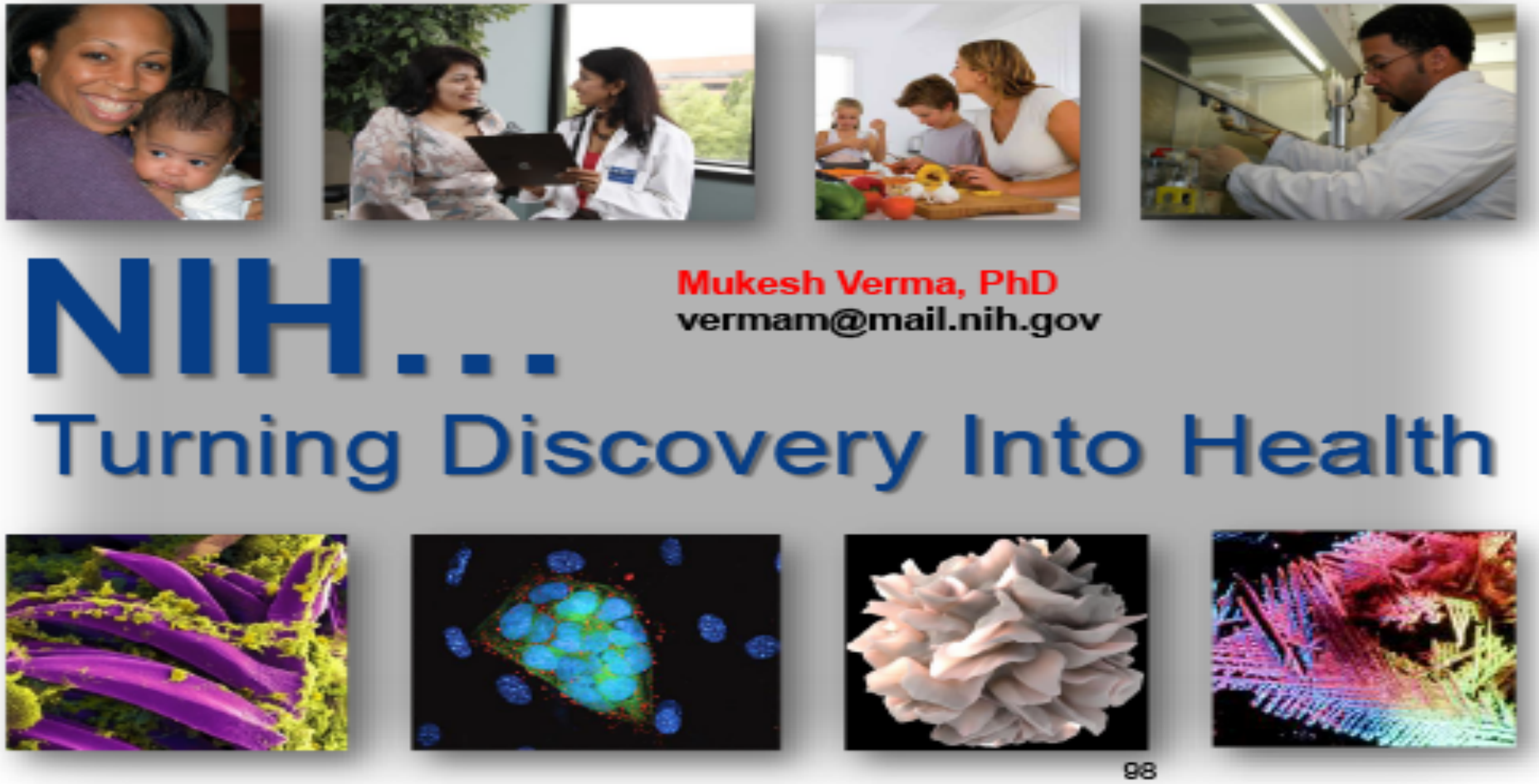
vide insights into
gly, investigators
current progress
literature and the
ds in epigenetics

research. We present a summary of the epidemiologic studies in NCI's grant portfolio from January 2005 through December 2012) and in the scientific literature published during the same period, irrespective of support from the NCI. Blood cells and tumor tissue were the most commonly used biospecimens in these studies, although buccal cells, cervical cells, sputum, and stool samples were also used. DNA methylation

Ongoing programs



NIH


NIH...
Mukesh Verma, PhD
vermam@mail.nih.gov
Turning Discovery Into Health
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